

BLACKWELL RESEARCH JOURNAL

June 2026 | Edition VII

Blackwell Research Institute

ISSN: 3066-8204

TABLE OF CONTENTS

1. The Psychological Impact of Hospital Volunteerism on Adolescents

Alexis Jay

2. Analysis of Forces that Affect Static Balances and Turns in Dance

Anna Lin

3. Pulsars as Tools for a Variety of Astrophysics

Annaliese Ebanks

4. Female-Specific Cognitive Trajectories in Neurodegeneration

Sahana Dayal Aravindakshan

5. Into the Quantum Era: Investigating Quantum Key Distribution's Role in Cybersecurity

Nishant Ambegaonkar

6. Alzheimer's Disease Diagnostic Methods: Techniques, Limitations, and Future Directions

Kolbi Herzfeld

7. Moderate-to-Severe Psoriasis: Advancing Skin Clearance through Novel Biologic Therapy

Scarlett Brez

8. Atherosclerotic Risk Factors and Their Impact on Brain Circulation After Cardiac Arrest

Areen Sandhu

9. Apollo to Artemis: How Past Spaceflight Disasters Shape Modern Space Missions

Alex Skillman

10. Understanding Cancer: Synopsis of the Incurable

Euni Kim

11. Little Molecule, Big Impact: How DNA Shapes Modern Medicine

Zelie Little

12. Genetic and Environmental Determinants of ACL Injury in Female Athletes: Implications for Targeted Prevention and Rehabilitation

Pierson Brant

13. fMRI-Based Deception Detection and Forensic Validity

Ilario Bonelli-Pentangelo

14. Medications for Treating REM Sleep Disorders Can Improve Memory Consolidation by Restoring Normal REM Sleep Function

Jianxi Zhou

The Psychological Impact of Hospital Volunteerism on Adolescents

Alexis Jay

Abstract: Hospital volunteerism is frequently positioned as a formative experience that cultivates adolescents' interest in healthcare careers; however, these environments also expose volunteers to emotionally demanding clinical realities. This case study examined whether psychological resilience mediates the relationship between emotional stress during hospital volunteerism and adolescents' healthcare career interest. Using a mixed-methods correlational design ($n = 42$), data were analyzed through descriptive, correlational, and mediation techniques, supplemented by thematic analysis. Emotional stress was negatively associated with both psychological resilience and healthcare career interest, while resilience was strongly positively associated with career interest. Psychological resilience fully mediated this relationship, as the direct effect of emotional stress became non-significant ($p = .314$) when resilience was included, with approximately 80.7% of the total effect transmitted through the indirect pathway. Qualitative findings further illustrated variability in adolescents' responses to emotionally demanding experiences, highlighting differences in how participants interpreted and managed exposure to medical trauma, patient suffering, and clinical uncertainty through adaptive coping strategies such as emotional regulation, cognitive reframing, and support-seeking. These results indicate that developmental and vocational outcomes of hospital volunteerism are shaped by differences in how adolescents psychologically process and adapt to emotionally intensive environments.

Introduction

Across the United States, thousands of teenagers volunteer in hospitals—pushing wheelchairs, delivering flowers, assisting staff, or interacting with patients and families. These experiences are often portrayed by school counselors and academic advisors as straightforwardly beneficial, serving to develop character, strengthen résumés, and inspire interest in pursuing healthcare careers. Yet, exposure to hospital hallways, marked by loss, uncertainty, illness, and emotional strain, may be psychologically demanding to adolescent volunteers, whose neurological development, emotional regulation, and identity formation are still maturing. Thus, exposure to high-pressure clinical environments introduces emotional demands that adolescents may be uniquely vulnerable to, making these experiences more complex than adults often assume.

Despite the prevalence of adolescent hospital volunteerism, there remains a notable lack of empirical data examining how adolescents psychologically interpret these experiences and how such emotionally demanding environments impact adolescents' mental health and healthcare career interest. In this absence, schools and healthcare institutions may continue to promote experiences that inadvertently

undermine students' well-being or long-term career motivation. This evidentiary gap leaves it yet to be established whether emotionally stressful volunteer experiences discourage teens from pursuing healthcare careers or—when met with sufficient psychological resources—deepen their vocational commitment to this field. Additionally, adolescence is characterized by heightened stress sensitivity due to ongoing neurodevelopment (Romeo, 2013), suggesting that emotionally demanding hospital environments may carry amplified psychological impact during this period. To address this complexity, the present study examines the relationship among perceived emotional stress experienced during hospital volunteerism, psychological resilience, and adolescents' self-reported interest in pursuing future healthcare careers. Rather than preemptively assuming healthcare volunteerism is psychodevelopmentally adaptive or maladaptive, this study investigates whether individual differences in psychological resilience account for how adolescents respond to emotionally demanding volunteer experiences in the hospital setting.

Literature Review

Psychological Resilience

According to the American Psychological Association (APA, n.d.), psychological resilience refers to the capacity to cope with, adapt to, and “bounce back” from emotionally strenuous experiences through flexible modulation of behavior in response to situationally varying intrapersonal and external pressures. Psychological literature conceptualizes resilience not as a fixed trait but as a dynamic process through which stressful experiences are cognitively and emotionally processed, shaping subsequent psychobehavioral outcomes (Luthar et al., 2000).

Research in healthcare contexts indicates resilience functions as both a protective psychological resource and a mediating mechanism through which stress exposure translates into psychological outcomes. Alhawtmeh et al. (2021), examining adult registered nurses during the COVID-19 pandemic, found that resilience mediated the relationship between perceived stress and quality of life. Rather than reducing stress exposure, resilience explained how stress influenced psychological outcomes, supporting mediation-based models in stress research. Similarly, Bovier et al. (2004) concluded that internal resources such as mastery and self-esteem shaped how perceived stress related to mental health outcomes, while Kwok et al. (2013) found that volunteer well-being in adults was influenced indirectly through psychological mechanisms like need satisfaction rather than stress exposure alone. Collectively, these studies suggest that resilience-related processes account for variability in responses to stress, underscoring resilience as an intermediary psychological process. While resilience research has largely concentrated on adults, comparatively little work has examined its function during adolescence—a period characterized by ongoing maturation of neuroemotional regulatory

and coping systems. This limitation is especially consequential in hospital volunteer settings, where adolescents may encounter emotionally demanding situations without the adequate psychoregulatory maturity typical of adults.

Emotional Stress

Emotional stress refers to “the feeling of psychological strain and uneasiness produced by situations of danger, threat, and loss of personal security or by internal conflicts, frustrations, loss of self-esteem, and grief,” (APA, 2018). In hospital volunteer settings, stress may arise from ongoing exposure to patient suffering, clinical uncertainty, or emotionally intensive interactions with patients, families, and healthcare personnel. Research consistently characterizes hospital environments as emotionally intensive, even for individuals not providing direct clinical care.

Studies of hospital volunteers indicate that repeated exposure to illness and vulnerability can generate sustained psychological strain. Ripamonti et al. (2018) concluded that volunteers who discontinued service reported significantly higher emotional exhaustion than those who remained active. However, volunteers who persisted often derived meaning from their roles, indicating that emotional stress alone does not uniformly predict outcomes. These findings suggest that stress is not inherently maladaptive; rather, its effects depend on how it is psychologically processed. Accordingly, stress may operate as an experiential input whose impact is shaped by intervening psychological mechanisms rather than functioning as a direct determinant of engagement or well-being.

However, existing literature overwhelmingly focuses on adults and emphasizes outcomes such as burnout or retention. Far less research examines adolescents, despite evidence that adolescence is characterized by ongoing neurobiological maturation—particularly of the hypothalamic-pituitary-adrenal (HPA) axis—which contributes to heightened stress reactivity, reflected in amplified emotional responses and less consistent regulatory control during this developmental period (Romeo, 2013). Thus, emotionally charged hospital environments may hold amplified developmental significance during adolescence, functioning not only as sources of emotional strain but also as contexts for inspiration and identity exploration.

As adolescents construct vocational identities, salient hospital encounters may shape emerging beliefs about competence, purpose, and professional fit, influencing future healthcare aspirations. Consequently, adolescents may experience hospital environments with greater intensity and variability than adults, potentially interpreting hospital-related stress in qualitatively distinct ways. However, research has not examined how emotional stress during hospital volunteerism influences adolescents’ psychological processing or subsequent outcomes like career motivation. Without accounting for developmental vulnerability, existing research cannot determine whether emotional stress discourages vocational interest or contributes to growth when mediated by

resilience.

Healthcare Career Interest

Healthcare career interest refers to the motivational inclination to pursue medical or allied health professions, characterized by curiosity, intention, and career self-efficacy. During adolescence, vocational interests are actively forming and are particularly responsive to experiential learning opportunities such as volunteering. Research on adolescent career development emphasizes exposure-based experiences as influential in shaping vocational interests. Muncan et al. (2016) argue that hospital volunteering may increase interest in medical careers by enhancing career awareness and providing an experiential context beyond abstract ideals. However, this work does not account for the emotional demands of hospital settings or the psychological processes through which exposure translates into sustained vocational motivation.

Longitudinal research suggests participation alone is insufficient to predict lasting vocational outcomes. Kim and Morgül (2017) found that voluntary service was associated with stronger long-term educational and civic engagement outcomes than involuntary service, indicating that how adolescents internalize volunteer experiences shapes developmental trajectories. Similarly, Ferreira et al. (2015) found that volunteers’ satisfaction and sense of meaningful contribution predicted intentions to remain involved in healthcare roles. Although primarily examining adults, these findings suggest that healthcare career interest is shaped not merely by exposure but by how experiences are interpreted, integrated, and incorporated into developing vocational identities.

Collectively, this literature indicates that vocational motivation emerges through psychological processing of experiential exposure rather than participation alone.

Despite these insights, little empirical research has examined how emotionally demanding hospital volunteer experiences influence adolescents’ healthcare career interest through these underlying psychological mechanisms, particularly when accounting for resilience.

Psychological Distress

Psychological distress reflects generalized emotional strain—including chronic stress, anxiety, and difficulty regulating emotions—that adolescents commonly experience across academic and social contexts. Robotham (2008) emphasizes that student populations often exhibit elevated baseline stress attributable to cumulative developmental and academic pressures.

In research examining context-specific stressors, failing to account for baseline distress may confound interpretations by obscuring whether reported strain originates from the focal environment or from broader emotional burden. Within hospital volunteerism, adolescents with higher baseline distress may report greater emotional strain or altered motivation independent of volunteer experiences. Accordingly,

psychological distress is included as a control variable to account for adolescents' baseline emotional functioning outside hospital contexts. Controlling for generalized distress allows for a more precise examination of stress specific to hospital volunteerism and clarifies the mediating role of psychological resilience in shaping healthcare career interest (Robotham, 2008).

Gap

Existing research establishes that hospital environments are emotionally demanding, as adolescents exhibit heightened stress reactivity due to ongoing neurodevelopment (Romeo, 2013), while psychological resilience mediates the relationship between stress and psychological outcomes in adult healthcare populations (Alhawtmeh et al., 2021). Scholarship on youth volunteering further suggests that exposure to healthcare settings can shape career interests, but outcomes depend on how experiences are psychologically processed (Muncan et al., 2016; Kim & Morgül, 2017). However, no empirical study has examined whether psychological resilience mediates the relationship between emotional stress during hospital volunteerism and adolescents' healthcare career interest. Accordingly, this study asks: To what extent does psychological resilience mediate the relationship between emotional stress experienced during hospital volunteerism and adolescents' interest in pursuing healthcare careers? It is hypothesized that resilience will mediate the association between emotional stress and healthcare career interest in adolescents. Specifically, emotional stress experienced during hospital volunteerism is expected to be associated with levels of psychological resilience, which in turn will be associated with adolescents' interest in pursuing healthcare careers. In this model, psychological resilience serves as the mediating mechanism linking emotionally demanding hospital volunteer experiences to adolescents' healthcare career motivation.

Methods

Research Design

This study employed a cross-sectional mixed-methods correlational survey design to examine whether psychological resilience mediates the relationship between emotional stress experienced during hospital volunteerism and adolescents' healthcare career interest. Quantitative survey data were used to examine statistical relationships among emotional stress, resilience, healthcare career interest, and baseline psychological distress. Qualitative responses were collected to provide contextual insight into adolescents' emotional experiences and coping strategies within hospital volunteer environments.

Data were collected using an anonymous electronic survey administered through Qualtrics. The survey included structured Likert-type items measuring the primary constructs and open-ended questions designed to capture participants' reflections on emotionally challenging volunteer

experiences and their perceived impact on career motivation. A complete, formatted copy of the survey instrument is included in Appendix A, and consent materials are included in Appendix B.

Participants & Recruitment

Participants were hospital volunteers ages 16–21 recruited from St. Joseph's Hospital (Tampa), AdventHealth (Carrollwood), and Tampa General Hospital (Tampa). Eligibility criteria required participants to be at least 16 years old and to have completed a minimum of three consecutive months of hospital volunteer service to ensure sustained exposure to hospital environments. Hospital volunteer coordinators distributed the anonymous survey link via email or in person.

Procedure & Implementation

Participants accessed the survey through an anonymous Qualtrics link. The survey consisted of four 10-item Likert-type scales and three optional open-ended questions (Appendix A). The quantitative measures assessed emotional stress during hospital volunteerism, psychological resilience, healthcare career interest, career decision self-efficacy, and overall psychological distress. Items were context-adapted from established instruments (e.g., PSS-10, CD-RISC-10, CDESES-SF) and modified to reflect hospital volunteer experiences (Appendix A).

All items used a 5-point Likert-type scale ranging from 0 (Strongly Disagree) to 4 (Strongly Agree). Composite scores were calculated by summing item responses within each scale, with higher scores indicating higher levels of the construct measured. Open-ended questions invited participants to describe emotionally challenging volunteer experiences, coping strategies, and recovery process, and reflections on how volunteerism influenced their interest in pursuing healthcare careers.

Ethical Compliance

Prior to beginning the survey, participants completed an eligibility screener and electronic informed consent (Appendix B). Participation was voluntary, and respondents were informed they could decline any question or withdraw from the survey at any time. To protect adolescent participant privacy, no personally identifying information was collected, individuals under age 16 were automatically exited, and all responses were analyzed in aggregate. Because the survey addressed potentially emotional hospital experiences, support resources were provided at the conclusion of the survey.

Data Screening & Preparation

Survey responses were screened for eligibility and completeness prior to analysis. Responses that did not meet eligibility requirements or contained incomplete quantitative survey data were excluded from the dataset. Open-ended questions were optional; therefore, participants were not excluded for missing qualitative responses. Only respondents with

complete quantitative data were retained for analysis.

Measures

Table 1 summarizes the constructs measured, their role within the mediation model, and the instruments used to adapt the survey items.

Statistical Analysis

Descriptive statistics, including means and standard deviations, were computed for emotional stress during hospital volunteerism, psychological resilience, healthcare career interest, and overall psychological distress to summarize central tendencies and variability across the primary study constructs. Composite scores were calculated by summing item responses within each scale (Appendix A). Pearson correlation analyses were conducted and presented in a Pearson correlation matrix to examine the strength and direction of linear associations among emotional stress, psychological resilience, healthcare career interest, and overall psychological distress. Overall psychological distress was included as a control variable to account for baseline emotional strain unrelated to hospital volunteering.

Internal consistency reliability for each multi-item scale was assessed using Cronbach's alpha coefficient (α), which evaluates the degree to which items within a scale measure the same underlying construct by examining average inter-item correlations. Values range from 0 to 1, with higher values indicating greater internal consistency. Consistent with conventional psychometric standards, $\alpha \geq .70$ was interpreted as acceptable reliability, $\alpha \geq .80$ as good reliability, and $\alpha \geq .90$ as excellent reliability. Reliability estimates were calculated for each scale prior to conducting the primary statistical analyses to ensure that the items within each scale demonstrated sufficient internal consistency for use in subsequent statistical analyses.

To test the proposed mediation model, regression analyses were conducted following the Baron and Kenny (1986) mediation framework, examining whether psychological resilience mediated the relationship between emotional stress during hospital volunteerism and healthcare career interest, while controlling for overall psychological distress. The mediation model evaluated the total effect of emotional stress on healthcare career interest (path c), the effect of emotional stress on psychological resilience (path a), the effect of psychological resilience on healthcare career interest while controlling for emotional stress (path b), and the direct effect of emotional stress on healthcare career interest after accounting for resilience (path c). The indirect effect ($a \times b$) was calculated to determine the extent to which psychological resilience explained the relationship between emotional stress and healthcare career interest. Regression coefficients (B), standard errors (SE), t-values, and p-values were reported for each mediation pathway to estimate effect size, sampling variability, and statistical significance. In addition, the proportion mediated was calculated to estimate the percentage of the total association between emotional

stress and healthcare career interest explained by the indirect pathway through psychological resilience. The significance of the indirect effect was evaluated using both a Sobel test and bootstrapping procedures with 5,000 resamples to generate bias-corrected 95% confidence intervals and estimate the indirect effect of emotional stress on healthcare career interest through psychological resilience. Bootstrapping is a nonparametric resampling technique that produces more robust estimates of indirect effects without relying on normality assumptions. The proportion of the total effect mediated was also calculated to estimate the percentage of the relationship between emotional stress and healthcare career interest explained by psychological resilience. Full statistical outputs, including correlation matrices and mediation models, are provided in Appendices D and E.

Qualitative responses were analyzed using inductive thematic analysis to identify recurring patterns in adolescents' emotional experiences, coping strategies, and reflections on healthcare career motivation. A summary of thematic coding and representative excerpts is provided in Appendix F.

Results & Findings

A total of 67 survey responses were collected among adolescent hospital volunteers. After applying eligibility criteria and removing responses with incomplete quantitative data, the final analytic sample consisted of 42 participants, whose responses were included in the quantitative analyses. Because open-ended items were optional, fewer participants provided qualitative responses, resulting in a smaller subset for thematic analysis.

Quantitative Findings

Descriptive Statistics & Scale Reliability

Descriptive statistics and internal consistency estimates were calculated for all study variables (Appendix C). Participants reported relatively low to moderate levels of emotional stress during hospital volunteerism ($M = 12.36$, $SD = 8.22$). This mean score indicates that responses generally fell in the lower to mid-range of the scale, corresponding to adolescents reporting occasional—but not consistently high—levels of emotional strain during volunteer shifts. The relatively large standard deviation reflects substantial variability in responses, indicating that while some participants reported minimal stress, others reported notably higher levels of emotional strain during hospital experiences.

Average levels of psychological resilience were relatively high ($M = 31.07$, $SD = 8.62$), as were healthcare career interest and career decision self-efficacy ($M = 30.05$, $SD = 9.21$). Higher mean scores were concentrated toward the upper end of the scale, reflecting strong confidence in coping with stress, adapting to challenges, and maintaining motivation toward healthcare careers. However, the variability suggests that, although many participants reported high levels of resilience and career interest, others reported more moderate or lower levels, resulting in a broader distribution of responses.

Table 1. *Variable-to-Measure Map*

Construct	Role in Model	Items	Higher Score Indicates	Adapted From
Emotional Stress During Hospital Volunteerism	Independent Variable (IV)	10	Greater volunteer-specific emotional stress	PSS-10, HADS, CAPDS-10
Psychological Resilience	Mediator	10	Greater resilience	CD-RISC-10, RSA/ARQ
Healthcare Career Interest & Career Decision Self-Efficacy	Dependent Variable (DV)	10	Greater healthcare interest/self-efficacy	CDSES-SF, SII
Overall Psychological	Control Variable (Covariate)	10	Greater baseline distress	CAPDS-10, PSS-10

Note. PSS-10 = Perceived Stress Scale–10; HADS = Hospital Anxiety and Depression Scale; CAPDS-10 = Children and Adolescents Psychological Distress Scale; CD-RISC-10 = Connor–Davidson Resilience Scale–10; RSA = Resilience Scale for Adults; ARQ = Adolescent Resilience Questionnaire; CDSES-SF = Career Decision Self-Efficacy Scale – Short Form; SII = Strong Interest Inventory. Items were adapted to reflect hospital volunteer experiences. Full survey items are provided in Appendix A, and reliability coefficients for each scale are reported in Appendix C.

This spread corresponds to differences in participants' reported consistency in managing emotionally demanding situations, adapting to unexpected clinical environments, and maintaining confidence in pursuing healthcare-related careers.

Mean overall psychological distress was 11.86 (SD = 9.66), indicating that responses generally fell toward the lower end of the scale, corresponding to relatively low levels of generalized emotional strain across the sample, while still reflecting variability in baseline distress among participants.

All scales demonstrated strong internal consistency reliability. Cronbach's alpha coefficients ranged from .85 to .92, exceeding the commonly accepted reliability threshold of 0.70. Emotional stress demonstrated good reliability ($\alpha = 0.85$), while resilience ($\alpha = .92$), career interest ($\alpha = .92$), and psychological distress ($\alpha = .92$) demonstrated excellent reliability. These coefficients indicate that items within each scale showed a high degree of consistency in how participants responded, supporting the use of composite scores for subsequent analyses.

Correlations

Pearson correlation analyses were conducted to examine relationships among emotional stress during hospital volunteerism, psychological resilience, healthcare career interest, and overall psychological distress (Appendix D). Emotional stress was significantly negatively correlated with psychological resilience, $r(40) = -.54$, $p < .001$, indicating that adolescents who reported greater emotional stress during hospital volunteerism tended to report lower levels of resilience. This relationship corresponds to a pattern in

which participants who more frequently endorsed feelings of emotional overwhelm, uncertainty, or exhaustion during volunteer shifts also tended to report lower agreement with items reflecting confidence in coping, adaptability, and emotional regulation. Emotional stress was also negatively correlated with healthcare career interest, $r(40) = -.49$, $p < .01$, suggesting that higher perceived emotional stress was associated with lower interest in pursuing healthcare careers. Specifically, this reflects that participants who reported more frequent or intense stress during hospital experiences were less likely to strongly endorse items related to motivation, confidence, or intention to pursue healthcare-related professions.

Psychological resilience was strongly positively correlated with healthcare career interest, $r(40) = .85$, $p < .001$, indicating that adolescents with higher resilience reported substantially greater interest in healthcare careers. This strong positive association corresponds to a consistent pattern in which participants who endorsed higher levels of coping ability, adaptability, and emotional control also reported higher levels of confidence in their ability to pursue healthcare careers and greater motivation to do so. Overall psychological distress was positively correlated with emotional stress, $r(40) = .37$, $p < .05$, suggesting that adolescents experiencing greater baseline distress also reported higher levels of stress during hospital volunteerism. This reflects that participants who more frequently endorsed general feelings of stress, anxiety, or emotional strain in daily life also tended to report increased stress within the hospital environment. However, distress was not significantly correlated with resilience or healthcare career interest.

Mediation Analysis

A mediation analysis using the Baron and Kenny approach was conducted to test whether psychological resilience mediated the relationship between emotional stress during hospital volunteerism and healthcare career interest, while controlling for overall psychological distress (Appendix E). First, emotional stress significantly predicted healthcare career interest, $B = -0.609$, $SE = 0.167$, $t = -3.66$, $p < .001$, indicating that higher stress was associated with lower healthcare career interest, corresponding to a pattern in which participants who more frequently reported emotional strain, overwhelm, or difficulty managing volunteer experiences were less likely to strongly endorse items reflecting motivation, confidence, or intention to pursue healthcare careers. Second, emotional stress significantly predicted psychological resilience, $B = -0.557$, $SE = 0.152$, $t = -3.66$, $p < .001$, suggesting that greater emotional stress was associated with lower resilience. This finding reflects that participants who reported higher levels of stress during hospital volunteerism also tended to report lower agreement with items reflecting adaptability, emotional regulation, and confidence in managing challenging situations. Third, psychological resilience significantly predicted healthcare career interest when controlling for emotional stress, $B = 0.883$, $SE = 0.105$, $t = 8.45$, $p < .001$. This corresponds to a consistent pattern in which participants who reported higher levels of coping ability and emotional regulation also reported stronger endorsement of healthcare career motivation, including confidence in their ability to pursue and succeed in healthcare-related roles.

When psychological resilience was included in the model, the direct effect of emotional stress on healthcare career interest became non-significant, $B = -0.118$, $SE = 0.115$, $t = -1.02$, $p = .314$, indicating full mediation, such that the relationship between stress and career interest was no longer statistically significant when psychological resilience was included in the model. This reflects that differences in career interest across participants corresponded more closely with differences in reported resilience than with stress levels alone.

The indirect effect ($a \times b$) was -0.492 , with approximately 80.7% of the total effect mediated through resilience, indicating that the association between emotional stress and healthcare career interest corresponded primarily to variation in psychological resilience rather than a direct relationship between stress and career interest, such that differences in participants' reported coping ability and adaptability aligned more closely with difference in healthcare career interest than differences in reported stress alone. A Sobel test confirmed the significance of the mediation effect ($Z = -3.355$, $p < .001$), demonstrating that the mediating pathway through psychological resilience was unlikely to have occurred by chance. Bootstrapping with 5,000 resamples further supported this finding, with a 95% confidence interval for the indirect effect of $[-0.706, -0.282]$, which

did not include zero, providing additional evidence that the indirect effect was consistently observed across resampled distributions of the data. Detailed regression outputs and indirect effect estimates are provided in Appendix E. Together, these results establish that psychological resilience fully mediates the relationship between emotional stress experienced during hospital volunteerism and adolescents' healthcare career interest.

Qualitative Findings

A thematic analysis of open-ended responses identified recurring patterns in adolescents' emotional experiences, coping strategies, and healthcare career motivations during hospital volunteerism (Appendix F). Three broad domains emerged: emotional stress encountered in hospital environments, coping processes reflecting psychological resilience, and variations in healthcare career interest.

Emotional Stress During Hospital Volunteerism

Participants reported exposure to emotionally challenging situations involving medical trauma, patient suffering, and uncertainty in high-intensity situations. Many described initial distress when encountering medical procedures, injuries, or bodily fluids for the first time. For instance, one participant stated, "Seeing someone get their gauze taken out of an open wound made me feel uneasy. It was my first time seeing that," suggesting that hospital environments often introduce adolescent volunteers to the physical realities of clinical care, which may initially function as significant emotional stressors.

Other participants described emotionally intense situations involving patient suffering or medical emergencies. Examples included witnessing seizures, hearing hospital code announcements, observing CPR, or encountering patients experiencing severe pain. In these situations, volunteers frequently reported uncertainty about how to respond due to limited clinical training or clearly defined roles. As one participant described, "I watched nurses and doctors perform CPR on a patient. It was very intense, and there were so many people in the room." Such responses suggest that emotional stress often arises when adolescents observe high-stakes medical events while lacking the authority or training to intervene.

Some volunteers also reported emotional strain when interacting with patients experiencing psychological vulnerability or emotional distress. Conversations with patients discussing loneliness, body image struggles, or the emotional consequences of illness were described as particularly impactful. However, a smaller subset of participants reported little or no emotional stress during their volunteer experiences, indicating that exposure to emotionally demanding situations may vary depending on volunteer assignments and individual perceptions of hospital environments.

Psychological Resilience and Coping Strategies

Participants described a range of strategies used to manage emotionally challenging experiences. Many adolescents reported using basic physiological regulation strategies such as deep breathing, taking brief breaks, or stepping away from stressful situations. One participant noted, “I take deep breaths and remind myself it’s okay.” These strategies suggest that volunteers frequently rely on immediate self-regulation techniques to restore emotional stability.

Social support from healthcare professionals also emerged as an important coping resource. Several participants described seeking reassurance or guidance from nurses, technicians, or other hospital staff when experiencing stress. In addition, some adolescents described cognitive coping strategies, such as reframing emotionally difficult experiences as preparation for future healthcare careers. One participant stated, “I coped by remembering that I’m going to have to experience these things if I want to become a healthcare worker.” Other participants described coping through distraction or emotional distancing after their volunteer shifts, while a smaller group reported using reflective practices such as journaling, prayer, or conversations with family members.

Healthcare Career Interest

Participants reported varied ways in which hospital volunteer experiences influenced their interest in pursuing healthcare careers. Many adolescents described volunteering as strengthening their motivation to work in healthcare, often citing interactions with patients and observations of healthcare professionals as inspiring experiences. For example, one participant explained, “Volunteering has made me more excited about a career in healthcare. I really like being able to make a difference.”

Some volunteers reported that their experiences increased their understanding of different healthcare roles and helped them explore potential career paths. Others described developing a stronger sense of empathy and a desire to help patients and families. However, a smaller number of participants indicated that exposure to medical trauma or emotionally demanding situations reduced their interest in hospital-based careers. One participant explained, “I don’t like it and don’t want to work at a hospital anymore after seeing the gory stuff.”

Overall, these qualitative findings illustrate that adolescents experience hospital volunteerism as emotionally complex and variable. While some participants reported increased motivation to pursue healthcare careers, others described emotional challenges that shaped their perceptions of clinical environments. Consistent with the study’s conceptual framework, participants’ responses suggest that the developmental impact of emotionally demanding hospital experiences may depend on how individuals cope with and psychologically process these encounters.

Discussion

Synthesis

The findings of this study provide a more integrated understanding of how emotional stress, psychological resilience, and healthcare career interest interact by clarifying how adolescents experience and respond to emotionally demanding hospital environments. Quantitative results indicated that emotional stress was negatively associated with both psychological resilience and healthcare career interest, while psychological resilience was strongly positively associated with healthcare career interest and fully mediated the relationship between emotional stress and career motivation. In conjunction with one another, these results suggest that the association between emotional stress and healthcare career interest was not direct, but rather contingent on differences in psychological resilience, such that stress was linked to reduced career interest primarily among adolescents with lower coping capacity, whereas this relationship attenuated as resilience increased.

The qualitative findings contextualize the nature of emotional stress by illustrating the types of adversity adolescents encountered during hospital volunteerism and how they processed these experiences. Participants described exposure to medical trauma, patient suffering, and uncertainty in high-acuity situations, often for the first time. While these stressors were relatively consistent across participants, their responses to these experiences varied substantially. Adolescents who described engaging in adaptive coping strategies—including cognitive reframing, emotional regulation, and seeking support from healthcare staff—reported sustained or increased interest in healthcare careers. In contrast, those who reported feeling overwhelmed or uncertain in these situations often described discomfort with hospital environments or decreased interest in pursuing healthcare roles. These patterns align with the quantitative correlations, suggesting that resilience functions as the mechanism through which stress is either integrated constructively or experienced as discouraging.

These differences in response reflect variation in psychological resilience. Participants who described using adaptive coping processes—including emotional regulation, cognitive reframing, and, in some cases, seeking support from healthcare staff—demonstrated more adaptive interpretations of emotionally demanding experiences. In contrast, participants who reported difficulty managing these experiences were more likely to describe discomfort with hospital environments or decreased motivation to pursue healthcare roles. These patterns suggest that resilience is not only an internal capacity but is reflected through how adolescents regulate, interpret, and respond to emotionally demanding situations.

Support-seeking emerged as one of several coping behaviors described in the qualitative data, rather than as a singular explanatory mechanism. Some participants reported asking healthcare professionals for reassurance or

clarification during stressful moments, while others relied on strategies such as emotional regulation, cognitive reframing, or reflective processing. Although help-seeking was not directly measured quantitatively, these responses suggest that it may represent one way in which resilience is enacted in practice. This aligns with research on adolescent coping that identifies help-seeking as an important component of effective stress regulation (Rickwood et al., 2007). However, the broader pattern indicates that resilience is multifaceted and expressed through a range of adaptive coping processes.

When considered alongside the quantitative findings, these qualitative patterns help explain why psychological resilience fully mediated the relationship between emotional stress and healthcare career interest. Adolescents exposed to similar levels of stress appeared to diverge in their career motivation based on how they processed those experiences. Those who were able to regulate, reinterpret, and make meaning from adversity were more likely to maintain or strengthen their interest in healthcare despite exposure to emotionally demanding clinical environments, whereas those who experienced stress as overwhelming were more likely to disengage.

Collectively, these findings support a process-based understanding of hospital volunteerism in which exposure to adversity does not uniformly lead to positive or negative outcomes. Instead, even when adolescents encounter emotionally demanding environments, the developmental and vocational impact of these experiences depends on how adolescents interpret and respond to them, with psychological resilience shaping this pathway.

Significance

These conclusions are significant because they challenge the widely held assumption that hospital volunteerism is uniformly beneficial for adolescents and instead demonstrate that outcomes vary based on how emotionally demanding experiences are processed. Prior research suggests that exposure to healthcare environments can increase career interest through experiential learning (Muncan et al., 2016) and that psychological resilience mediates the relationship between stress and outcomes in adult healthcare populations (Alhawtmeh et al., 2021). However, these studies do not account for the variability in adolescents' emotional responses to hospital environments or the mechanisms through which these experiences influence career motivation.

By integrating these perspectives, the present study contributes a more refined, process-based understanding of adolescent development within healthcare volunteer settings. Specifically, the findings show that exposure alone does not correspond to consistent developmental outcomes; instead, the relationship between hospital experiences and career interest depends on how adolescents psychologically interpret and respond to emotionally demanding situations. This distinction is critical in real-world contexts. School counselors, academic advisors, and volunteer coordinators

often recommend hospital volunteering as a way to build character and inspire career interest, yet these findings indicate that such outcomes are conditional rather than guaranteed. Adolescents who are not equipped with strategies to manage emotionally demanding situations may experience reduced confidence or disengagement, while those who engage in adaptive coping processes may develop increased motivation and clarity in their career goals.

This study, therefore, extends existing research by demonstrating that resilience in adolescents operates not only as a psychological mediator but as a process reflected in observable coping behaviors. By juxtaposing these findings with prior literature, this research highlights a gap in existing assumptions about volunteer experiences and provides a more actionable framework for understanding how such experiences correspond to different developmental outcomes. In doing so, it shifts the field from an exposure-based model to a process-based model, emphasizing that the benefits of hospital volunteerism depend on how adolescents are supported in interpreting and managing these experiences.

Limitations

Several limitations should be considered when interpreting these findings, particularly in relation to replicability and generalizability. First, the sample was geographically limited to hospitals in West Florida, which may restrict the extent to which these findings generalize to other regions with different healthcare systems, patient populations, or volunteer structures. Replication in varied geographic contexts is necessary to determine whether these patterns hold across different environments. Second, the study focused exclusively on adolescents aged 16–21, excluding younger individuals who may differ in emotional development, stress reactivity, and coping strategies. As a result, the findings cannot be extended to younger adolescent populations without further investigation. Third, the composition of the sample introduces potential gender bias. A substantial portion of participants (24 out of 42) were recruited from a single hospital through a school-affiliated healthcare volunteer organization composed primarily of female student volunteers. This overrepresentation may limit the applicability of the findings to more gender-diverse populations and may influence observed patterns in coping processes and emotional responses. Additionally, the use of a convenience sampling approach may affect replicability, as future studies using different recruitment methods may yield different distributions of responses.

The relatively small sample size ($n = 42$) also limits the stability and generalizability of the findings. While statistically significant relationships were identified, larger sample sizes would allow for more precise estimates and more robust mediation analyses. However, the use of bootstrapping procedures in the mediation analysis strengthens the reliability of the indirect effect estimates by reducing dependence on normality assumptions and improving the stability of results in smaller samples. Nevertheless, replication with larger

sample sizes remains necessary to confirm the consistency of these findings. Furthermore, the cross-sectional design limits the ability to assess how these relationships evolve over time. Longitudinal research is needed to assess the consistency of these patterns across repeated exposure to hospital environments.

Finally, while this study identifies help-seeking as a potential sub-construct of psychological resilience, it was not directly measured using a validated quantitative scale. As a result, conclusions regarding help-seeking are based on qualitative patterns and should be interpreted as preliminary. Future studies that explicitly measure help-seeking behaviors would improve replicability and allow for more precise examination of their role within the mediation model.

Future Directions

Future research should build on these findings by further examining the mechanisms through which adolescents interpret and respond to emotionally demanding healthcare environments. Longitudinal research is needed to assess how emotional stress, psychological resilience, and healthcare career interest interact over time, particularly as adolescents gain continued exposure to hospital settings. Such designs would allow researchers to determine whether coping processes and resilience develop with experience or remain stable across time.

Replication with larger and more diverse samples across multiple geographic regions and healthcare systems is also necessary to enhance generalizability. Future studies should aim to include more balanced gender representation and broader recruitment sources to ensure that findings are not disproportionately influenced by specific populations or institutional contexts. Expanding the age range to include younger adolescents may further clarify how the developmental stage influences emotional processing and coping.

Importantly, future research should further operationalize psychological resilience as a process by incorporating validated measures of specific coping behaviors, including—but not limited to—support-seeking. Examining how different coping strategies correspond to variations in stress processing and career motivation would provide greater precision in understanding the mechanisms underlying the observed relationships. Experimental or quasi-experimental designs may also be used to examine how structured support systems—such as mentorship programs, training, or guided reflection—affect adolescents' ability to navigate emotionally demanding experiences and sustain healthcare career interest.

Finally, continued use of validated multi-item scales, composite scoring procedures, and mediation analysis frameworks will support comparability across studies and strengthen replicability. By addressing these areas, future research can extend the present findings and provide a more comprehensive understanding of how emotionally demanding volunteer experiences shape adolescent development and

vocational trajectories.

Conclusion

This study investigated whether psychological resilience mediates the relationship between emotional stress experienced during hospital volunteerism and adolescents' healthcare career interest. Quantitative findings indicated that emotional stress was negatively associated with both psychological resilience and healthcare career interest, while psychological resilience was strongly positively associated with career interest and fully mediated the relationship between stress and career motivation. Notably, the direct effect of emotional stress on career interest becomes non-significant when resilience was included in the model ($p = .314$), with approximately 80.7% of the total effect transmitted through the indirect pathway. These results indicate that the impact of emotionally demanding volunteer experiences on career interest was shaped less by stress exposure alone than by differences in how adolescents interpreted and responded to those experiences. Qualitative findings further reinforced this pattern, showing that adolescents exposed to similar hospital stressors did not experience them uniformly: while some described these encounters as overwhelming or discouraging, others interpreted them as meaningful, formative, or motivating.

Collectively, these findings suggest that the developmental and vocational value of hospital volunteerism is not determined by exposure alone, but by the adaptive coping processes through which adolescents manage emotionally demanding clinical environments. Accordingly, psychological resilience functions not simply as an internal trait, but as a dynamic process that shapes whether stress is integrated constructively or experienced as discouraging. This reframing challenges the assumption that hospital volunteerism is inherently beneficial for adolescents and instead supports a process-based model in which outcomes depend on how these experiences are interpreted and managed. Although further longitudinal and more diverse replication studies are needed, the present findings provide an empirically grounded framework for understanding how emotionally demanding volunteer experiences can differently shape adolescent healthcare career motivation and developmental trajectories.

References

- Alhawatmeh, H., Alsholol, R., Dalky, H., Al-Ali, N., & Albataineh, R. (2021). Mediating role of resilience on the relationship between stress and quality of life among Jordanian registered nurses during COVID-19 pandemic. *Heliyon*, 7(11), e08378. <https://doi.org/10.1016/j.heliyon.2021.e08378>.
- American Psychological Association. 2018. "Emotional Stress." *APA Dictionary of Psychology*. <https://www.apa.org/topics/emotional-stress>.
- American Psychological Association. n.d. "Resilience." *APA Dictionary of Psychology*. <https://www.apa.org/topics/resilience>.
- Betz, N. E., Klein, K. L., & Taylor, K. M. (1996). Evaluation of a

- short form of the Career Decision-Making Self-Efficacy Scale. *Journal of Career Assessment*, 4(1), 47–57. <https://doi.org/10.1177/106907279600400103>
- Bovier, P. A., Chamot, E., & Perneger, T. V. (2004). Perceived Stress, Internal Resources, and Social Support as Determinants of Mental Health among Young Adults. *Quality of Life Research*, 13(1), 161–170. <http://www.jstor.org/stable/4038149>.
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24(4), 385–396.
- Connor, K. M., & Davidson, J. R. T. (2003). Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depression and Anxiety*, 18(2), 76–82. <https://doi.org/10.1002/da.10113>.
- De Stefano, C., Laurent, I., Kaïndje-Fondjo, V. C., Estevez, M., Habran, E., Falissard, B., Haag, P., Khireddine, I., D'Hont, F., Baubet, T., Oppenchain, N., Vandentorren, S., & Rezzoug, D. (2022). Children and adolescents psychological distress scale during COVID-19 pandemic: Validation of a psychometric instrument (CONFADO study). *Frontiers in Psychiatry*, 13, 843104. <https://doi.org/10.3389/fpsy.2022.843104>.
- Ferreira, M. R., Proença, T., & Proença, J. F. (2015). Volunteering for a Lifetime? Volunteers' Intention to Stay in Portuguese Hospitals. *Voluntas: International Journal of Voluntary and Nonprofit Organizations*, 26(3), 890–912. <http://www.jstor.org/stable/44668758>.
- Friborg, O., Hjemdal, O., Rosenvinge, J. H., & Martinussen, M. (2003). A new rating scale for adult resilience: What are the central protective resources behind healthy adjustment? *International Journal of Methods in Psychiatric Research*, 12(2), 65–76. <https://doi.org/10.1002/mpr.143>.
- Gartland, D., Bond, L., Olsson, C. A., Buzwell, S., & Sawyer, S. M. (2011).
- Development of a multi-dimensional measure of resilience in adolescents: The Adolescent Resilience Questionnaire. *BMC Medical Research Methodology*, 11, 134. <https://doi.org/10.1186/1471-2288-11-134>.
- Kim, J., & Morgül, K. (2017). Long-term consequences of youth volunteering: Voluntary versus involuntary service. *Social Science Research*, 67, 160–175. <https://doi.org/10.1016/j.ssresearch.2017.05.002>.
- Kwok, Y. Y., Chui, W. H., & Wong, L. P. (2013). Need Satisfaction Mechanism Linking Volunteer Motivation and Life Satisfaction: A Mediation Study of Volunteers Subjective Well-Being. *Social Indicators Research*, 114(3), 1315–1329. <http://www.jstor.org/stable/24720310>.
- Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development*, 71(3), 543–562. <https://doi.org/10.1111/1467-8624.00164>.
- Muncan, B., Majumder, N., Tudose, N. (2016). From high school to hospital: how early exposure to Healthcare affects adolescent career ideas. *International journal of medical education*, 7, 370–371. <https://doi.org/10.5116/ijme.5801.f2cc>.
- Rickwood, D. J., Deane, F. P., & Wilson, C. J. (2007). When and how do young people seek professional help for mental health problems?. *Medical journal of Australia*, 187(S7), S35–S39. <https://doi.org/10.5694/j.1326-5377.2007.tb01334.x>.
- Ripamonti, C. A., Pasquarelli, L., Ravasi, S., & Sala, F. C. (2017). Dropout of Hospital Volunteers in Italy. *Voluntas: International Journal of Voluntary and Nonprofit Organizations*, 28(1), 44–68. <http://www.jstor.org/stable/26160641>.
- Robotham, D. (2008). Stress among Higher Education Students: Towards a Research Agenda. *Higher Education*, 56(6), 735–746. <http://www.jstor.org/stable/40269100>.
- Romeo R. D. (2013). The Teenage Brain: The Stress Response and the Adolescent Brain. *Current directions in psychological science*, 22(2), 140–145. <https://doi.org/10.1177/g/0963721413475445>.
- Strong, E. K., Jr. (1994). Strong Interest Inventory manual. Consulting Psychologist Press.
- Wilson, J., & Musick, M. (1999). The Effects of Volunteering on the Volunteer. *Law and Contemporary Problems*, 62(4), 141–168. <https://doi.org/10.2307/1192270>.
- Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67(6), 361–370.

Analysis of Forces that Affect Static Balances and Turns in Dance

Anna Lin

Abstract: Dance is an athletic art form in which the dancer is constantly in conversation with forces. Understanding how they interact with these forces in different body positions can help improve technique both functionally and aesthetically; however, dance schools frequently neglect teaching the physics of forces that affect dancers. While some teachers provide conceptual insight on alignment, they do not share a deeper knowledge of specific forces. This study intends to analyze the forces that impact dancers in balances and turns. The literature review involved researching a variety of academic studies that were conducted with dancers at various ages and levels as they performed balances and turns en pointe and demi-pointe. In many of the studies, researchers analyzed forces through computer programs. They discovered that to successfully perform balances, dancers must achieve proper alignment of their center of mass over their base of stability. To maintain balance and maximize revolutions in a turn, torque must be correctly generated to achieve the angular momentum necessary to cleanly execute the step. In both static and dynamic balances, studies consistently noted transferring weight and momentum as a critical aspect. If dancers learn how forces impact fundamental steps such as balancing and turning, they can focus on how it applies to their own dancing to improve their technical abilities.

Keywords: forces, dance, center of mass, balance, turn

Introduction

Balancing and turning are fundamental skills that classical ballet dancers must be capable of performing successfully. They are present in every piece of choreography; therefore, they are essential for dancers to execute well. Failure at achieving alignment, exerting the wrong amount of torque, or being unable to fully transfer weight

or momentum can produce an unstable balance or turn.

Balancing in a variety of positions that distribute their body mass differently requires a dancer to find their center of mass (the point in which one's distribution of mass is at an equilibrium) relative to their weight distribution. The most relevant of these positions in classical ballet include retiré (a dancer's toe of their working leg touches the knee of their supporting leg), arabesque (a dancer's working leg extends directly behind them), attitude devant (a dancer's working leg extends directly in front of them and bends at the knee), and attitude derrière (a dancer's working leg extends directly behind them and bends at the knee). In ballet, these positions are always performed in a turned out position (rotation from the hips) and en relevé (a position in which the heel is lifted off the ground as a dancer balances on their toes). The relevé can be either en pointe (weight is on the toe in a fully extended position) or demi-pointe (weight is on the ball of the foot). Balances in retiré, arabesque, and attitude are prominent in grand adage, pas de deux, and turns.

The aim of the literature review is to provide conceptual understanding on forces that affect ballet dancers. When balancing in different positions, finding their center of gravity relative to their distribution of mass and the center of mass over their base of stability (the area in which one is in contact with the ground) allows dancers to stay lifted in their position and maintain balance. Adding torque to a balance during the initiation phase (while a dancer prepares) and shifting momentum allows a dancer to turn. The actions of forces are always the same; however, varying positions change the way a dancer interacts with them. If dancers are conscious of force interactions, they can accomplish key steps in classical dance with improved technique.

This review focuses on analyzing a variety of academic studies on both professional and pre-professional dancers' abilities to turn or balance and how their weight, alignment, or momentum affects their performance. Understanding the variety of forces that affect dancers when balancing or turning in different positions is crucial to executing the steps with correct technique.

Aligning Center of Mass Over Base of Stability in Static and Dynamic Balances

When dancers balance in any position, they must properly align themselves to maintain their center of balance. A dancer's posture must fundamentally remain consistent between positions; however, the way that their body responds to each varies (Lorenzi, 2011). Dancers should directly align their ankle, hip, and shoulder along a vertical axis such that their center of mass remains precisely over their base of stability for both static balances and balances while turning. The alignment of the upper body alone can shift in specific extended positions, such as an attitude derrière or arabesque to equalize the mass of the extended leg.

En pointe, a dancer's base of stability has a much narrower area compared to on demi-pointe. This leaves them with less margin of error and makes it difficult to stay balanced. Dancing en pointe also requires a further weight shift to align the center of mass over the base of stability since the base en pointe is further away from the dancer's midline than in a demi-pointe position.

Additionally, a dancer's center of mass differs depending on the position they are in. For example, in a position with their leg extended behind them, such as an arabesque, the dancer needs to shift their weight further forward by moving their chest and arms

toward their supporting leg. In contrast, a dancer balancing in a retiré will keep their upper body vertically positioned relative to their lower body.

In order to find and maintain balance in turns, dancers must hold and stabilize their body. They should activate muscles especially in their pelvis, core, and upper back during the turn phase (the period in which a turn actively occurs) of a pirouette (Dykstra et al., 2025). When dancers engage the muscles surrounding these areas with a focus on their weight shift, it allows them to hold their balance and place their center of mass over their supporting base.

If a dancer falls off balance, changing either the placement of their base of stability or adjusting their center of mass allows them to realign their body to stay on balance. A dancer can change positions of a part of their body to save their balance by either shifting their feet to adjust their contact area with the floor or changing the position of their torso, working leg, or arms to shift their center of gravity (Gollin, 2000). Altering their foot placement adjusts the dancer's base of stability, and rearranging their upper body changes the placement of their center of mass.

Dancers can align their posture with muscle memory as they respond to forces. Finding and maintaining balance requires reactive control (responding to disturbances in posture by adjusting the body's position), predictive control (anticipating disturbances in posture and preparing adjustments in advance), or a combination of both (Tsubaki et. al, 2024). Predictive control occurs during the initiation phase of a turn or balance. Reactive control arises during the turn phase or active balance. Predictive forces allow a dancer to set up their balance for proper alignment before execution while reactive forces allow them to maintain their balance once they are up. Ultimately, as dancers find their balance, maintaining their center of mass over their base of stability is crucial.

Relationship Between Torque and Angular Momentum in Turns

Turning is a movement necessary to dance repertoire that involves maintaining balance while rotating about a vertical axis. Dancers can generate torque (any twisting force that can cause rotation) for their turns in a variety of ways that affect their angular momentum, which is the product of angular velocity (the rate of rotation around a given axis) and moment of inertia (the body's tendency to resist acceleration of angular velocity).

Torque is commonly generated as the upper back and arms engage and push around in a turn. While the upper body is important for generating torque, the use of the lower body, including hips and feet, are also essential. When a dancer turns, they exert a horizontal force against the floor; Newton's third law states that the floor then pushes with an equal and opposite force (Laws, 1978). The push of opposite forces is a source of external torque for dancers when they initiate a turn. Proper use of turnout as dancers rotate their hips outward to push off the ground is another method to generate torque while maintaining stability. Different amounts of torque or techniques of generating it affect the magnitude and direction of the dancer's angular momentum and affect a dancer's success in the execution of their turn.

Researchers analyzed the relationship between torque and angular momentum across different types of turns, including pirouettes en dehors and en dedans, fouetté turns, and piqué turns. The total angular momentum only changes when it is acted upon by external torque. When angular momentum is at a constant and torque ceases

during the turn phase, the rate of the turn can be controlled by distributing mass relative to the rotation axis. Moment of inertia decreases by bringing any part of the body closer to the rotation axis which increases the angular velocity but keeps the angular momentum at a constant (Laws, 1978).

Once a dancer is already in their turn phase, they can no longer change the action of predictive forces or the quantity of the torque that they generated in their turn initiation phase. External torque is the only force that changes the dancer's angular momentum in a turn (e.g., partnered turns in which the partner pushes the dancer around).

Redistributing mass during a turn requires either bringing arms or legs closer to their axis of rotation (e.g., crossing arms instead of holding them *en avant* or leg in *cou-de-pied* instead of *attitude*) to increase the rate of the turn by decreasing moment of inertia and increasing angular velocity. Inversely, extending limbs (e.g., holding arms in *allongé* instead of *en avant* or extending leg to *arabesque* from *passé retiré*) slows the rate of the turn by increasing moment of inertia and decreasing angular velocity, while angular momentum remains constant.

In *fouetté* turns (a coda turn in which a dancer begins with a traditional *pirouette en dehors* and performs a *rond de jambe* with their working leg while their supporting leg *pliés* to *relevé* between each rotation), frictional torque is the only present external torque. *Fouetté* turns require both frictional torque (the greatest possible torque that friction can provide before a dancer slips) and twisting torque (any torque that allows a dancer to turn and, in *fouetté* turns, is typically generated by the working leg doing a *grand rond de jambe* in combination with the closing of the arms from a *la seconde* to *en avant*) (Imura and Yeadon, 2010). Frictional torque in *fouetté* turns affects a dancer's angular momentum; therefore, this affects their ability to turn on a vertically aligned axis of rotation.

Dancers generate torque through a variety of ways of engaging their muscles in turns, all of which affect their moment of inertia, angular velocity, and total angular momentum.

Transfer of Weight or Momentum in Dance Movement

In order to perform turns and static balances with correct technique, dancers are required to transfer weight and/or momentum. Through a proper shift, dancers can change their center of gravity and their relationship to forces. All dance steps share the principle of weight transfer from one part of the body to another, and shifting rotational or linear momentum is necessary to effectively execute them (Laws, 1998).

While proper technique for dancers also requires an aesthetic component, the mechanics of dance movements depend primarily upon momentum transfer. Furthermore, as the functionality of dance technique improves, studies have found that it also frequently helps dancers with the visual appearance of dance steps, especially in transitional movement.

While a dancer is in motion, their position changes their relationship to gravity; however, the physics of gravity itself remains constant (Coates and Demers, 2019). Because dancers' distribution of mass changes between positions, they shift their center of gravity changing how they interact with the forces around them.

If balancing or turning are specifically considered, a ballet dancer's control over their center of pressure (average location of the variation in pressure) is related to their control over their point

of contact (the area in which they are touching the floor) (Fronczek–Wojciechowska, 2016). Control over the center of pressure produces successful static and dynamic balances as well as a cleaner aesthetic. In any type of balance, a dancer's control over their point of contact allows them to control their center of pressure. Dancers should shift their weight to align their center of pressure with their contact point.

Dancing *en pointe* also affects weight and momentum shifts. Vertical ground reaction force (the weight of the body's action toward the ground) during the initiation phase of a *pirouette* allows dancers to complete a rotation when they effectively shift their center of mass upward. Ground reaction forces increase when turning in *pointe* shoes as opposed to flat shoes because of the rigidity of the outsole and the further upward movement (Tsubaki et al., 2024). The way that a dancer prepares for their turn affects the success of the turn itself.

With steps executed both *en pointe* and *demi-pointe*, transferring weight and momentum is critical for technical performance in dance.

Discussion

To successfully perform a balance or turn in ballet, dancers must first understand the forces that affect them. In this paper, studies were analyzed for alignment, stability, and external forces. Many other papers specifically analyzed dancers when balancing in either a static or dynamic state while only a few considered both. The aim of this study is to further explore the specific forces that affect dancers in static balances or turns and how they can correctly achieve them. Because balancing and turning are critical to dance, ballet dancers should have a more expansive knowledge on the physics of these steps. Ballet teachers should be committed to learning about the forces that affect dance movements and explaining them to their students to help less experienced dancers improve.

As they balance, dancers must learn to properly position themselves and make microadjustments with their muscles so that their center of mass stays in line with their base of stability. This helps them to complete a stronger and more stable balance with the alignment of their head, shoulder, pelvis, and ankle on their supporting side. Placement of the body, however, varies based on the distribution of weight in different positions. While differences based on distribution are mentioned in studies, there are no specific details regarding what changes needed to be made between positions other than general concepts on upper body in extended positions *devant* (working leg is extended to the front) versus *derrière* (working leg is extended to the back).

In dynamic balance during a turn, dancers still should achieve and maintain their balance, but they must additionally generate torque to rotate. Torque can be produced using both upper and lower body which suggests that both engaging the back and arms as well as holding rotation in the hips in the initiation phase can increase angular momentum during the turn phase. When performing both static and dynamic balances, dancers must correctly transfer weight or momentum. Comprehending these concepts of weight transfer and force can be a primary factor that progresses a dancer to exceptional technique.

While studying forces is important, there are still many other factors that should be considered. Every dancer is built differently, so they must learn how to apply what they learned to their individual bodies to improve their technique. There is also not much informa-

tion available that compares balances between different positions specifically en pointe as many of the studies were performed on demi-pointe. While general concepts remain consistent throughout available sources, more research needs to be done to provide expanded information on details, such as equations to model the forces specifically in dance movement or a focus on distinct steps instead of general concepts. It may also be beneficial to study how biomechanics affects forces so that dancers can better understand how to apply the knowledge of physics to their bodies and dancing.

Conclusion

As forces are further studied for their effect on dancers in static and dynamic balances, dancers should be educated on the impact of physics to help them improve their technique both physically and aesthetically. If dancers fail to intentionally interact with the forces that affect their movement, then the step will be performed with incorrect technique and with increased difficulty. Their center of mass and base of stability should orient on a vertical axis in any balancing position. When turning, dancers must maintain vertical alignment while also generating torque. These dance movements all require a correct weight and momentum transfer to perform them successfully. Ultimately, dancers interact with a variety of forces when performing steps. These concepts could be taught in the context of existing conditioning classes or wellness seminars at dance schools where dancers are already learning more intellectually and physically about their bodies. Teaching the physics of dance would implement an additional level of training that can help dancers to feel stronger in some of the most fundamental movements in dance repertoire.

References

- Coates, E., & Demers, S. (2019). *Physics and Dance*. Yale University Press. <https://doi.org/10.2307/j.ctv8jnzz0>
- In a book published in 2019 by Emily Coates and Sarah Demers from Yale University, they use models and activities to show how gravity acts upon a dancer. This is relevant to the forces affecting dancers because it explains how gravity remains the same; however, a dancer's position changes their relationship to it as each of their limbs moving changes their center of mass. However, it does not specifically focus on ballet turns; it takes a more general approach to dance.*
- Dykstra, A.; Kooistra, A.; Merucci, N.; Zeitler, D.W.; Alderink, G. The Margin of Stability During a Single-Turn Pirouette in Female Amateur Dancers: A Pilot Study. *Appl. Sci.* 2025, 15, 7519. <https://doi.org/10.3390/app15137519>
- Annalisa Dykstra (et al.) from Grand Valley State University in Grand Rapids, Michigan published a paper in 2025 analyzing dancers of varying levels, between ages of 18 and 40, through videography and photography footage of their performance of and margin of stability in pirouettes. This relates to ballet turns because it emphasizes the ways in which dancers must maintain their center of mass over their base of support in pirouettes. However, it does not note much the impact of forces on these turns.*
- Gollin, G. (2000, June 21). The Physics of Dance. *Physics in Engineering at Illinois*. https://hep.physics.illinois.edu/home/g-gollin/dance/dance_physics.html#10
- In an article by George Gollin from the University of Illinois, he took a group of dancers that was around him and observed their performance of different ballet steps. This is relevant to forces that affect a dancer's turns and balance because it provides insight on opposite forces allowing for stability and the impact of gravity, torque, and friction as a dancer remains over their center of mass with a small point of contact on the floor.*
- Imura, A., & Yeadon, M. R. (2010). Mechanics of the Fouetté turn. *Human movement science*, 29(6), 947–955. <https://doi.org/10.1016/j.humov.2010.08.002>
- Akiko Imura (et al.) of the University of Tokyo and M.R. Yeadon of Loughborough University published a paper in 2010 over the mechanics of the fouette turn by using a computer simulation model. This is relevant to the forces that affect a dancer's turns because it includes the relationship between limiting frictional torque and turning torque and how the coordination relates to a dancer's rotation. They found that their results also applied to pirouettes and grand fouettes en tournent.*
- Laws, K. L. (1978). An Analysis of Turns in Dance. *Dance Research Journal*, 11(1–2), 12–19. doi:10.2307/1477841
- In this analysis from 2014, Kenneth Laws from Cambridge University studied how factories such as center of balance, torque, and angular momentum affect a ballet dancer in performing a turn. This paper relates to how different forces affect dancers while turning en pointe in different positions through the insight it provides on how friction, horizontal force, and inertia impact dancers in various turns. While it does not directly touch on different kinds of turns, it contains a variety of differences in how torque and momentum are affected between pirouettes en dehors or en dedans, en pointe or demi-pointe, and in a traditional retire position or extended position (i.e., arabesque, attitude, or a la second).*
- Laws, K. (1998). Momentum Transfer in Dance Movement. *Medical Problems of Performing Artists*, 13(4), 136–145. <http://www.jstor.org/stable/45440343>
- In a 1998 publication by Kenneth Laws through the Medical Problems of Performing Artists journal, Laws studied how different methods of performing turns affected a dancer's momentum. This is relevant to how forces affect ballet turns because it illustrates how proper ballet technique ensures the correct relationship of forces to properly perform turns including pirouettes, fouettes, and partnered turns (pirouettes, whip turns, and finger turns).*
- Lorenzi, M. G. (2011). Physics in dance and dance to represent physical processes.
- In a 2011 publication in the Journal of Applied Mathematics by Marisa Michelini, she observed ballet students ages 15–16 performing pirouettes en pointe and created models and equations from this. This is relevant to the physics of ballet turns because it explains how dancers must maintain equilibrium in a pirouette over a small supporting base and considering that once a dancer accelerates and enters the turning phase, they can only adjust their angular velocity. Additionally, their center of mass also changes with the position of their limbs given that the human body is not rigid.*
- Magdalena Fronczek-Wojciechowska, Gianluca Padula, Joanna Kowalska, Manuela Galli, Salvatore Livatino & Karolina Kopacz (2016) Static balance and dynamic balance related to rotational movement in ballet dance students, *International Journal of Performance*

Analysis in

Sport, 16:3, 801-816

In this 2016 analysis by Magdalena Fronczek-Wojciechowska (et al.), 9 “junior” dancers and 4 “senior” (more experienced) dancers from a ballet school in Poland were analyzed in their center of pressure displacement and velocity in static balances and various turns en pointe and demi pointe. This is applicable to forces that affect balances and turns en pointe and demi-pointe; however, it primarily only focuses on the center of pressure as opposed to a wider range of forces.

Tsubaki Y, Kawano Y, Lin C-F, Kuno-Mizumura M. Differences in the Rotation Axis Between Professional and Experienced Amateur Ballet Dancers During pirouette en de-hour in Classical Ballet With Wearing Pointe Shoes: A Pilot Study. *Journal of Dance Medicine & Science*. 2024;28(1):43-50. doi:10.1177/1089313X231206432

In a 2024 study by Yurina Tsubaki et al., both professional and amateur dancers were observed for their CoP-CoM vertical angle and vertical reaction force when performing single pirouettes en pointe. This is relevant to forces that affect dancers while turning en pointe because it specifically analyzed dancers turning en pointe and recorded their vertical reaction forces and center of pressure.

Pulsars as Tools for a Variety of Astrophysics

Annaliese Ebanks

Abstract: In recent years, pulsars have been used to study a variety of astrophysical properties. Pulsars are a branch of neutron stars that are known for their incredibly fast rotation speed and reliable pulse periods. Millisecond pulsars and magnetars are sub types of pulsars that add depth to the study of pulsars and other extreme objects of gravity. Pulsars can be studied in a multitude of ways. Scientists look at the light curve, take censuses, and use radio wavelengths to study them. Many observatories, like EPTA, SKA, LIGO, and LISA are committed to observing them to further advance pulsar study. In this review, I will explore pulsars from many different angles to find that pulsars are a wonderful tool to provide valuable insight into gravitational waves, mapping the interstellar medium of the Milky Way, and the nature of neutron stars.

Keywords: Pulsars, gravitational waves, neutron stars, light curves, Milky Way

The discovery of pulsars has forever changed the field of astrophysics. Pulsars are the key to mapping the universe and finding celestial bodies. Many observatories are committed to studying them and finding all their hidden characteristics. The observations of pulsars greatly impact our understanding of a variety of astrophysical processes that will be discussed in this review.

To understand pulsars, it is important to start with understanding the story of stars.

Figure 1 from (Aller 2026) displays stellar evolution.

Figure 1 illustrates that stars can live very different lives depending on their mass and metallicity, which is essentially the

presence of elements heavier than hydrogen and helium in a star's composition. A star with a lower mass evolves and eventually ejects gas outward to form a planetary nebula with a white dwarf at the center. On the other hand, stars with higher masses continue to get larger until they go supernova. A supernova is a stellar explosion that indicates the death of a star and possible birth of a celestial body in which mass, metallicity, composition, and energy are deciding factors. For example, if the mass is over 25 solar masses, a black hole, an object whose density allows no escape, is born (Carroll and Ostlie 2007). If it is lower than that, the explosion forms a neutron star. Heger et al. (2003) finds, “At lower metallicities, roughly 20% massive stars form black holes and roughly 75% form neutron stars.” The story of stars provides a background for all stars. Given the many studies across the neutron stars across the sky, scientists have uncovered a diverse array of properties about these objects and the supernovae they come from.

Neutron stars are the result of Type IIp supernovae. During these supernovae, the core of the star collapses and then explodes outward, leaving behind an incredibly dense, compact object. When they are observed, Type IIp supernovae are noted for their rapid rise in luminosity (Carroll and Ostlie 2007). Neutron stars are one of the densest objects known to mankind. A neutron star's average density is approximately 3.7×10^{17} to 6.65×10^{17} kg/m³ (Carroll and Ostlie 2007). This would mean a teaspoon of a neutron star weighs as much as the human population. Their size is the antithesis: The average neutron star is roughly 10-20 kilometers, the same size as Manhattan.

The extreme density of a neutron star prevents scientists from replicating their material in labs. Many properties, such as the equation of state, are unknown, which pushes forward further study of these objects. Not only are pulsars used to discover more unrevealed qualities about neutron stars and other space objects, but they are also utilized as tests for fundamental physics and laboratories of extreme gravity.

This literature review will be organized as follows. In Section 2, pulsars will be defined, and their characteristics will be discussed. Section 3 will discuss all things of observation in relation to pulsars. The applications of pulsars will be listed in Section 4. Section 5 will summarize key points and mention future projects.

Section 2: Pulsars

Radio pulsars were discovered by Jocelyn Bell and Antony Hewish at Cambridge in 1967 (Hewish et al. 1968). Pulsars are a subsection of neutron stars known for quick rotation speed and the emittance of regular periodic radiation along the magnetic field.

Figure 2: A schematic of the magnetic field and radio emission of a spinning pulsar. As a reminder, the presence of a magnetic field in a pulsar is exceedingly important. As the pulsar spins around its rotation axis so does the emitted light along the poles, causing a “lighthouse” effect. The “lighthouse” effect in a pulsar is a perfect example of synchrotron radiation. Electrons are pulled to the magnetic field and accelerated. Whenever an electron is accelerated or its energy changes, it releases light. That's how the pulsar light beams are produced. The magnetic field is directly proportionate to the electrons release of light. The stronger the magnetic field, the more powerful the release of light. (Figure from: Bell Burnell 2017).

The violent birth of a pulsar in supernovae yields its high velocity. The spin period of a pulsar ranges from 1.4 milliseconds

to 8.5 milliseconds (Manchester et al. 2001). Pulsar period rotation is extremely consistent, but it is not exactly constant. While sudden glitches are not likely, they are possible. In addition to its spin period, a pulsar's spin down is equally important. Spin down is the moderate decline in rotation speed that is caused by the loss of kinetic energy. Their decreases are small, but over a long period, they can be noticeable.

Pulsars address countless scientific goals. Some major goals from Cordes et al. (2005) include:

- Map the Milky Way and properties of the galactic center
- Identify the equation of state of super dense matter
- Discover extrasolar planets
- Probe intergalactic medium in new ways

In addition to addressing scientific goals, pulsar study has awakened many challenging questions scientists are attempting to solve. Cordes et al. (2005) lists a few:

- What are the minimum and maximum spin periods for radio pulsars?
- How are isolated millisecond pulsars produced?
- What is the relationship between core collapse and neutron star birth properties?
- Do the magnetic fields of isolated neutron stars decay?

2.2 Types of Pulsars

Magnetars are slow-moving and highly magnetized pulsars that are known for a wide display of X-ray activity. Magnetars were noticed by astronomers in the late 1970s when X-ray instruments aboard the Venera 11 and 12 picked up on activity. They get their name from the decay of an immensely strong internal magnetic field (Kapsi and Beloborodov 2017). Magnetars typically have a spin period of 5 to 8 seconds (Carroll and Ostlie 2007). Their spin-down period suggests a younger age than normal pulsars. Because of the many unique properties magnetars exhibit, they add to the depth of characterizing the wide range of pulsars.

Millisecond pulsars are a branch of pulsars that spin at a quicker speed. Though they are both types of neutron stars, there are a wide range of differences between a regular pulsar and a millisecond pulsar. To begin with, the spin behavior of these two types is different. A millisecond pulsar's average rotation speed is recorded as less than 10 milliseconds. Because millisecond pulsars have incredibly fast pulses that make them more reliable, they provide a great way to study gravitational waves, which will be discussed in Section 4 (Carroll and Ostlie 2007). Binarity is another contributing factor in their contrasts. Lorimer writes, "Orbiting companions are observed around 80% of all millisecond pulsars but less than 1% of all normal pulsars" (2009). Companions are, usually, white dwarfs or other neutron stars. Lastly, it is observed that millisecond pulsars have a notably smaller birth rate than normal pulsars.

Section 3: Observation

With their unique rotation speed and beams of light, there are numerous observatories researching pulsars currently. The whole scientific world is collaborating to discover and use these fast-spinning stars with observatories such as EPTA, SKA, LIGO, and LISA.

3.1 Observational Techniques

It is important to study pulsars; as such, the more pulsar detections, the more rare objects astronomers can utilize as physics laboratories. Pulsars are detected at radio wavelengths. Radio observatories observe the periodic peak in light emission, which is most easily studied in the radio wavelength, but can be observed in different wavelengths for specific details. Observatories, like the SKA, perform censuses of the Milky Way galaxy and other galaxies to gain more knowledge of the layout of them. In fact, scientists from the SKA predict that a pulsar census will map the Milky Way (Cordes et al. 2005). In addition, a Galactic census can be used to estimate birth rates for millisecond and binary pulsars. To be successful, observatories must have multiple frequency sensors to detect pulsars.

Figure 3: The light curve of a pulsar. In addition to other methods, astronomers primarily utilize light curves to observe pulsars. Light curves illustrate the emittance of light over time. Astronomers use this because it demonstrates the periodic emittance of a pulsar, and it assists in visualizing any discrepancies in light emittance. Light curves are distinct and signature to each pulsar. However, light curves have features that are alike (Figure from: Cerutti et al. 2016).

3.2 The European Pulsar Timing Array

The European Pulsar Timing Array, commonly known as EPTA, provides valuable contributions to the worldwide goal of gravitational wave detection and pulsar research. Located in Europe, EPTA contains five of the largest cm radio telescopes in the world. Kramer and Champion (2013) describe the following:

Lovell Telescope: A 76.2-meter radio dish in northwest England, which has compiled an extensive library of pulsars over the years.

Nançay Decametric Radio Telescope: A transit telescope built in 1965 that has made over 15,000 observations since the start of EPTA.

Westerbork Synthesis Radio Telescope: A telescope located in the Netherlands that is operated by ASTRON and offers a wide range of frequencies.

Effelsberg Radio Telescope: A 100-meter radio telescope located 30 km southwest of Bonn, which has a powerful back end.

Sardinia Radio Telescope: A completely steerable dish located in the south of Sardinia at 700 meters in elevation, which has a dual frequency that allows it to operate at 2 different hertz.

To give an example of their findings, EPTA researchers concluded that PSRJ1811 has too slow of a spin to be a useful pulsar timing array, but there is more data to draw from it with its potential to be a double neutron star system (Kramer and Champion 2013).

3.2 SKA

The SKA observatory, or the SKAO, will deeply impact radio astronomy and pulsar study as a whole. The observatory is unique because it has two telescopes on two different continents. The SKA-low is in Australia, and the SKA-mid is in South Africa. The SKA Observatory pulsar census has uncovered pulsars with diversity in qualities such as spin, magnetic field, and evolutionary stage (Joshi et al. 2025). Joshi and the SKA Pulsar Science working group write, "population synthesis models predict that the Milky Way hosts

more than 50,000 active pulsars” (2025).

3.3 LIGO and LISA

In the past few years, the missions of LIGO and LISA have caused excitement in the astrophysical community. Danzmann from the LISA study team, writes, “LISA is a laser-interferometric gravitational wave detector in space designed to observe gravitational wave signals from galactic as well as cosmological sources in frequency range from 0.1 mHz to 1 Hz” (2000). LISA is estimated to be commissioned within the next decade. LIGO, also referred to as Laser Interferometer Gravitational Wave Observatory, seeks to detect and observe gravitational waves that come from space (LIGO Collaboration Team 2009). While they are helpful to pulsar research, LIGO and LISA’s general goal is to detect and observe gravitational waves. In addition to merging or spinning black holes, rapidly spinning neutron stars can also emit gravitational waves the LIGO and LISA are able to detect. This adds an additional perspective to observe pulsars.

3.4 Observational Challenges

Pulsars in their abnormality present many observational challenges. First, one big problem scientists are trying to tackle is pulsar nulling. When the distance between pulses gets larger, the neutron star is dying as an active or useful radio pulsar. This can make it harder to understand pulsar mechanisms. Second, radio intermittency poses another problem. Radio intermittency describes the behavior of radio sources that are not frequently active. These erratic inconsistencies can confuse and interrupt data. For instance, a pulsar with on and off cycles is nicknamed a “sometimes” pulsar (Kramer et al. 2006). Scientists use this type to learn more about neutron star physics. Third, the emission beam of a pulsar is finite in size. Only a fraction of the population is visible to scientists. The angle of a pulsar’s beam in relation to earth is paramount. Different amounts of light will be distributed based off the Earth’s location. Though they are never ending, scientists are constantly working to tackle these challenges.

Section 4: Application

4.1 Gravitational Waves

An important use of pulsars is gravitational wave detection. Albert Einstein’s General Theory of Relativity has been tested continually since its creation. Chris Faesi best simplified it when he wrote, “The presence of matter causes the fabric of spacetime to curve, and the motion of massive objects causes this curvature to change with time” (2012). Gravitational waves, disturbances in the fabric of spacetime with small amplitudes, are a great source to test this theory. As of now, pulsars are one of the best ways to detect gravitational waves because of the accuracy at which scientists can determine their pulses of light. Any deviation from the known period of these pulsars could be caused by a ripple in the spacetime it is travelling through, otherwise known as a gravitational wave. Any deviation in a pulse caused by a gravitational wave, big or small, can be calculated and determined here on earth. Many people in the astrophysics community argue in favor of using a Pulsar Timing Array to detect gravitational waves (McWilliams et al. 2012).

4.2 Pulsars as Maps

Along with similar observational methods, pulsars can be used to analyze the ISM or the space between stars, otherwise known as the Interstellar Medium. Pulsars emit light in consistent periodic ways, so anything along astronomers’ line of sight to the pulsar can affect this periodic signature. In this way, astronomers learn about objects in the sky between Earth and these pulsars by observing how they affect periodic signals from the pulsar. For example, if the signal changes for a short time, there might have been something along the line of sight that changed. It doesn’t always necessarily have to be a gravitational wave; it could be due to a denser region of space, like a nebula, passing along the line of sight which can then be mapped. Pulsars are used as maps by utilizing their light emittance and pulses as GPS signals.

4.3 Pulsars as the Key to Knowing More About Neutron Stars

Lastly, pulsars can be used to reveal more about neutron stars themselves. First, observing various properties of pulsars allows scientists to model the structure and interiors of the extreme objects that are neutron stars. Cordes et al. writes, “The discovery of even smaller rotational periods will provide significant insight into the properties and stiffness of the ultra-dense liquid interior of NSs (neutron stars)” (2005). In addition to that, glitches, a spin up in rotational speed followed by slow relaxation, also probe the interior of a neutron star by revealing superfluidity; superfluidity, in relation to stars, refers to the absence of viscosity and friction in a neutron star core. Next, scientists can also use pulsars to find the equation of state for neutron stars and other high-density objects. In summary, the unknown qualities of neutron stars can be discovered by studying and observing pulsars.

Section 5: Conclusion

In conclusion, pulsars are tools that scientists can use to increase knowledge of astrophysical processes. Pulsars are a subsection of neutron stars noted for their reliable rotation period and unique magnetic field. Types of pulsars, like magnetars or millisecond pulsars, reveal much about their qualities and characteristics. Pulsars can be detected by using radio wavelengths. Scientists observe pulsars by studying light curves and taking censuses of a given population. Important observatories like EPTA, SKA, LIGO, and LISA are extremely impactful to pulsar study. In this specific review, pulsars have been shown to be useful tools that detect gravitational waves, probe the expanse of space and its celestial bodies, and uncover the extreme environment of neutron stars.

With the commission of numerous projects and the construction of many observatories, the astronomical community has a lot to be excited about. First, Five-hundred-meter Aperture Spherical Radio Telescope, also known as FAST, has been constructed in China and has made a lot of new discoveries. Second, gravitational wave detectors like LIGO and LISA have caused a lot of commotion because of their features and design. While LIGO is out and operating, LISA will not be in commission until 2035. As a result of the many observatories and projects set into motion, scientists expect to learn much about pulsars in the upcoming years.

References

Abbott, B. P., Abbott, R., Adhikari, R., Ajith, P., Allen, B., Allen, G., Amin, R. S., Anderson, S. B., Anderson, W. G., Arain, M. A., Araya, M., Armandula, H., Armor, P., Aso, Y., Aston, S.,

Female-Specific Cognitive Trajectories in Neurodegeneration

Sahana Dayal Aravindakshan

- Aufmuth, P., Aulbert, C., Babak, S., Baker, P., ... Zweizig, J. (2009). LIGO: the Laser Interferometer Gravitational-Wave Observatory. *Reports on Progress in Physics*, 72(7), 076901. <https://doi.org/10.1088/0034-4885/72/7/076901>
- Becker, W. (2009). *Neutron stars and pulsars*. Springer.
- Bell Burnell, J. (2017). The past, present and future of pulsars. *Nature Astronomy*, 1(12), 831–834. <https://doi.org/10.1038/s41550-017-0323-x>
- Cerutti, B., Philippov, A. A., & Spitkovsky, A. (2016). Modelling high-energy pulsar light curves from first principles. *Monthly Notices of the Royal Astronomical Society*, 457(3), 2401–2414. <https://doi.org/10.1093/mnras/stw124>
- Cordes, J. M., Kramer, M., Lazio, T. J. W., Stappers, B. W., Backer, D. C., & Johnston, S. (2004). Pulsars as tools for Fundamental Physics & Astrophysics. *New Astronomy Reviews*, 48(11–12), 1413–1438. <https://doi.org/10.1016/j.newar.2004.09.040>
- Danzmann, K. (2000). Lisa Mission Overview. *Advances in Space Research*, 25(6), 1129–1136. [https://doi.org/10.1016/s0273-1177\(99\)00973-4](https://doi.org/10.1016/s0273-1177(99)00973-4)
- Faesi, C. (2012, November). The race to detect gravitational waves: Pulsar timing arrays | astrobit.es. <https://astrobit.es/2012/11/23/the-race-to-detect-gravitational-waves-pulsar-timing-arrays/>
- Fernie, J. D. (2026, January 20). Star - formation, evolution, lifecycle | britannica. *Britannica*. <https://www.britannica.com/science/star-astronomy/Star-formation-and-evolution>
- Heger, A., Fryer, C. L., Woosley, S. E., Langer, N., & Hartmann, D. H. (2003). How massive single stars end their life. *The Astrophysical Journal*, 591(1), 288–300. <https://doi.org/10.1086/375341>
- Hewish, A., Bell, S. J., Pilkington, J. D., Scott, P. F., & Collins, R. A. (1968). Observation of a Rapidly Pulsating Radio Source. *Pulsating Stars*, 5–9. https://doi.org/10.1007/978-1-4899-6387-1_1
- Information@Eso.org. (n.d.). Light curve of Crab Pulsar. www.eso.org/public/images/eso9948i/
- Joshi, B. C., Karastergiou, A., Burgay, M., & Pulsar Science Working Group. (2025). Pulsar science with the SKA observatory. *The Open Journal of Astrophysics*, 8 Supplement(1). <https://doi.org/10.33232/001c.154638>
- Kaspi, V. M., & Beloborodov, A. M. (2017). Magnetars. *Annual Review of Astronomy and Astrophysics*, 55(1), 261–301. <https://doi.org/10.1146/annurev-astro-081915-023329>
- Kramer, M., & Champion, D. J. (2013). The European Pulsar Timing Array and the large European array for pulsars. *Classical and Quantum Gravity*, 30(22), 224009. <https://doi.org/10.1088/0264-9381/30/22/224009>
- Lattimer, J. M. (2015). Introduction to neutron stars. *AIP Conference Proceedings*, 1645, 61–78. <https://doi.org/10.1063/1.4909560>
- McWilliams, S. T., Ostriker, J. P., Pretorius, F. (2012). The imminent detection of gravitational waves from massive black-hole binaries with pulsar timing arrays. https://ui.adsabs.harvard.edu/link_gateway/2012arXiv1211.4590M/doi:10.48550/arXiv.1211.4590

Abstract: Alzheimer’s disease often affects women disproportionately compared to men, where nearly two-thirds of all Alzheimer’s cases affect women. A unique paradox that women face is that they initially have a higher cognitive baseline, but then subsequently face a steeper decline in cognitive function. While this paradox masks symptoms and results in diagnosis later in the disease course for women, it ultimately leaves women more vulnerable to the disease. This study aims to identify the different social and biological factors that leave women more vulnerable to Alzheimer’s disease and neurodegeneration. This paper includes a comprehensive review of data presented in different research and review articles about how female-specific factors influence the disease’s progression. It was found that the higher cognitive baseline in women masks early symptoms of Alzheimer’s, making it difficult for early intervention. In addition, there are many different brain structural differences in the male and female brain that can contribute to the steep cognitive decline. Finally, female specific life stages, like menopause and pregnancy, could potentially increase risk of developing Alzheimer’s later in life. Understanding the different drivers that contribute to the steep decline is crucial for implementing better diagnostic and clinical testing for Alzheimer’s disease in women.

Introduction

Alzheimer’s disease is one of the most common forms of dementia worldwide. Every year, Alzheimer’s kills more people than breast cancer and prostate cancer combined. As the Baby Boomer’s generation age and life expectancy increases, the number of people diagnosed with Alzheimer’s is expected to drastically rise. Women tend to be more affected by Alzheimer’s disease. Nearly ¾ of all Alzheimer’s cases worldwide affect women. One reasonable explanation is that women simply live longer, thus making women more prone to developing Alzheimer’s. However, Alzheimer’s disease is a very complex and heterogeneous disorder, influenced by a combination of biological and environmental factors.

Women face a very peculiar paradox when it comes to cognitive decline. Women have better verbal memory and a higher cognitive baseline compared to men, and also tend to maintain cognitive function longer than men. Although women preserve their cognitive function better into old age, they experience a sudden and aggressive decline.

This review explores why women face such a sharp decline despite having a higher cognitive baseline, and what factors make women more vulnerable to developing Alzheimer’s disease. In this article, I will discuss the multitude of genetic and lifestyle factors that are responsible for this phenomenon. I will examine how memory can mask early symptoms, sex-differences in brain anatomy, and female-specific life events that can contribute to cognitive decline. Understanding these patterns and female-specific trajectories will allow researchers and clinicians alike to improve diagnosis and treatment of women with Alzheimer’s disease.

Masking Effect

The phenomenon of women going from a higher verbal memory to a rapid decline can be primarily explained by the masking effect. Cognitive baseline is an individual's healthy level of mental function that can be measured through cognitive tests examining memory, problem solving skills, and attention. This cognitive baseline serves as a reference for future cognitive testing that can help define disease progression for dementia. On average, women typically outperform men in verbal memory and episodic memory, thus setting their baseline higher^{2,8}. Verbal memory, the ability to learn and recall memory of verbally presented information, and episodic memory, the ability to remember every-day events, are usually the first cognitive functions to decline in Alzheimer's disease^{6,8}. Verbal memory and episodic memory stay stable in women throughout their adulthood⁶.

According to the cognitive reserve theory, women's high cognitive baseline and verbal memory may act as resistance factors, allowing women to maintain normal cognition for longer, even after the disease has started. Since many Alzheimer's tests use verbal recall to identify cognitive dysfunction, clinicians are unable to detect the disease in women. Women can function better despite the higher burden of neuropathology compared to men in early stages. Essentially, these initial strengths serve as a clinical shield, preventing the identification of the early signs of Alzheimer's Disease².

Clinicians are often unable to detect early Alzheimer's in women because of their higher cognitive baseline and higher verbal memory compared to men⁶. This often leads to a delayed diagnosis, specifically in Mild Cognitive Impairment (MCI), a precursor to developing symptoms of dementia. Most cognitive diagnostic tests use a one-size-fits-all approach to testing that fails to properly take sex into account. Due to this oversight, approximately 10% of MCI cases are missed in women^{2,6}. When sex is not taken into account, women's scores appear within normal range, even if they might have experienced some cognitive decline. This trend also results in higher rates of men getting falsely diagnosed with MCI as they score lower in the normal range². By the time clinicians do diagnose women, in many cases, it is very late⁶. Failing to take sex into account limits opportunities for early intervention in women.

Once the brain's masking affects wear off, women's brains reach a tipping point. Once their brains have exhausted their defenses, women face a steep and aggressive decline^{6,8}. Women facing cognitive decline reach significant impairment thresholds (0.5-SD lower than normal cognition) around 4.72 years earlier than men⁸. In addition, this rapid decline adds the equivalent of 5 to 6 years of cognitive aging to a woman's profile compared to a man of the same age⁸. Taken together, women's steep decline can be explained by late identification of cognitive changes and thus late diagnosis, effectively preventing women from potential early intervention.

Brain Structure Differences

Beyond diagnostic delays, underlying biological blueprints further separate how the female and male brain respond to Alzheimer's pathology⁵. Women appear to have an overall lower initial grey matter volume compared to men. While men have an overall higher volume of gray matter, women have thicker cortices and larger relative volumes of gray matter when adjusted for skull size^{2,8}. Although initially an advantage cognitively, this eventually makes them more vulnerable to the breakdown that happens once

Alzheimer's pathology occurs^{2,8}. In addition, women diagnosed with Alzheimer's disease or MCI show increased atrophy rates of up to 1.5% per year compared to men, which means women go through a more accelerated degeneration². This is particularly evident in the hippocampus, a critical memory center, which shows more pronounced atrophy in women as the disease progresses². While women initially show greater cognitive resilience to hippocampal volume loss, their brain deteriorates much faster when reaching the tipping point². The structure of a woman's brain helps with cognition initially, but also succumbs much more rapidly to Alzheimer's and dementia compared to men.

Differences in white matter distribution between men and women also support selective vulnerability to neurodegeneration in women. This is especially apparent in the burden of small vessel disease. White matter hyperintensities, which are markers of small vessel disease and vascular damage, are found more and with bigger volumes in women compared to men¹¹. Cerebrovascular damage can drive faster declines in executive function and processing speed that aren't necessarily explained by Alzheimer's pathology¹¹. The higher burden of small vessel disease means that women have fewer defenses to fight against neurodegeneration¹¹, which may explain why the decline is so steep.

Sensitivity to Age-related Neuropathology

The brain's reaction to toxic pathologies differs from sexes, especially when we are considering tau pathology. Women consistently show lower resistance to tau, and are more prone to amyloid pathology. Women have significantly higher levels of tau pathology across multiple regions of the brain⁵. This is critical because tau is a hallmark of Alzheimer's and deposition of pathogenic tau is strongly correlated with cognitive decline⁹. In women, the association between tau and developing Alzheimer's and other forms of dementia is higher than in men⁵. This suggests that women are much more sensitive to the presence of tau accumulation.

In addition, women tend to suffer more from mixed or co-pathologies. This can be where the pathological hallmarks of Alzheimer's co-exists with other neurodegenerative aggregates such as Lewy bodies or TDP-43². These other pathologies act as another attack on the brain, further contributing to the steep decline that women face².

Sources take different routes when explaining the female's brain verbosity to toxic tau. One source talks about how the female brain has more interhemispheric connectivity compared to men. Given the fact that disease-associated forms of tau spread through synaptically connected neurons⁸, the female brain's anatomy can allow for a more rapid and widespread distribution of tau². Another source notes that the correlation between the burden of tau and verbal memory decline is stronger in women⁶. Both of these are reasonable explanations to how toxic tau pathology can contribute to the steep decline.

Female Specific Life-Stages

The third cause of the steeper decline is due to life factors that uniquely affect the female cognitive resilience trajectory. Menopause is a major biological turning point for women in which they experience a permanent end to menstruation and fertility during their late 40s and early 50s. After menopause, women experience a sharp decrease in the hormone estrogen, specifically estradiol, by up to 90%. The hormonal shift is a trigger for rapid

cognitive decline in women, as estradiol is critical for supporting blood vessels, neural repairs, and exerts anti-inflammatory and antioxidant effects in the brain⁷. This makes it an incredibly important cognitive shield for women¹. Women who experience an early or surgical menopause have a significantly higher risk of cognitive decline and a greater burden of AD pathology^{1,6}.

Female-specific cardiovascular risks that happen early in their life can have an impact on their brain's health¹. One of the most significant markers of this is an adverse pregnancy or preeclampsia. Such complications due to high blood pressure can be a critical predictor of future cognitive decline¹. Pregnancy puts significant strain on the cardiovascular system, and such strain is associated with greater white matter damage in the brain later in life^{1,2}. In addition, because the cardiovascular side effects of pregnancy are not always considered in typical clinical testing, this can bolster the delayed diagnoses and false negatives that women face¹.

Lifestyle Factors

Lifestyle factors can be interpreted differently according to different sources. Some look at lifestyle factors on an individual level, such as social visits or partners. Others take a broader view to look at sociocultural shifts.

Education is one of the most helpful lifestyle factors that enhances cognitive resilience². Women's cognitive function increases from education more compared to men in areas such as memory resilience and higher baseline performance². Historically, education is highly gendered, meaning that women are at a disadvantage when it comes to that means of resilience^{2,6}.

Other physical and social lifestyle factors that play a role in women's cognitive reserve are exercise, socialization, and mental health. Exercise can be more physically beneficial to women than men, thus making exercise a critical factor in physical and cognitive resilience in women³. For example, high levels of daily walking have been associated with larger hippocampal volumes in women, but not in men³. For women, frequent social visits with friends and family have also been related with higher cognitive resilience¹⁰. Living with someone else is also a predictor of cognitive resilience¹⁰. However, because women typically live longer than men and are expected to outlive their partners, they are more likely to face social isolation later in life¹⁰. Mental health plays a significant role in overall brain health. Women are diagnosed with depression twice as often as men⁴. Depression is associated with smaller hippocampal volumes and faster volume loss, particularly in the female brain⁴. Collectively, women experience a specific set of life factors that may also contribute to their vulnerability to neurodegeneration.

Discussion

The female paradox of higher verbal memory to a steeper cognitive decline is a result of a multitude of biological and social factors, including the masking effect, different biological triggers, female-specific life stages, and lifestyle factors. The masking effect occurs when the higher cognitive baseline of a woman masks early signs of cognitive decline, since diagnostic testing of early symptoms is typically not sex-specific. This leads to delayed diagnosis, making chances for early intervention and treatment not possible. Biological factors include having less grey matter compared to men, higher burden to small vessel disease, and more sensitivity to tau pathology. This leads to a higher vulnerability to neurodegenera-

tion. Female specific life-stages, such as pregnancy and menopause, can contribute to the steep decline due to the high stress burden they can place on the body. Indeed, adverse pregnancy outcomes or an early/surgical menopause can be future predictors of neurodegenerative diseases. Finally, different lifestyle factors can uniquely shape the cognitive resilience trajectory, particularly in regard to economic status, education, and community engagement.

Better understanding of women's health is crucial to improving treatment for women experiencing neurodegeneration and age-related cognitive decline. In the future, clinicians and neurologists should emphasize earlier cognitive testing for women, and redefine comparative baselines. Comparative cognitive baselines typically account for both men and women as a "one size fits all", and do not account for the sex differences discussed in this paper. However, factoring in the multiple biological and social factors that could contribute to Alzheimer's and understanding female-specific patterns may allow clinicians to be able to detect Alzheimer's in women before progressive decline sets in. While the pathology underlying neurodegenerative diseases such as Alzheimer's generally begins decades before symptom onset, earlier intervention and treatment can improve patient outcomes and quality of life.

Women's health is historically understudied, and thus misunderstood, however lack of participant diversity further weakens our understanding. In many of the studies, the participants were primarily non-Hispanic Whites. In addition, many of them were well-educated. Furthermore, many studies don't have participant diversity in areas such as gender identity, race/ethnicity, and socioeconomic background. Future research needs to push for diverse recruitment in order to enhance our current knowledge and ultimately drive forward progress in how we approach and treat neurodegeneration.

References

- Alexander, M. W., Paterson, J., Arvanitakis, Z., Black, S. E., Casaletto, K. B., Christakis, M. K., Einstein, G., Galea, M., Harwood, L., Kirkham, A., Mitchell, S., Pa, J., Perri, L., Splinter, L., Swardfager, W., VandeBunte, A. M., & Rabin, J. S. (2025). Cardiovascular contributions to dementia: Examining sex differences and female-specific factors. *Alzheimer's & Dementia*. <https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/alz.70610>
- Arenaza-Urquijo, E. M., Boyle, R., Casaletto, K., Anstey, K. J., Vila-Castelar, C., Colverson, A., Palpatzis, E., Eissman, J. M., Kheng, T., Raghavan, S., Muge Akinci, Vonk, J., Machado, L. S., Zanwar, P. P., Shrestha, H. L., Wagner, M., Stefano Tamburin, Sohrabi, H. R., Loi, S., & Bartrés-Faz, D. (2024). Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimer's & Dementia*. <https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.13844>
- Barha, C. K., Davis, J. C., Falck, R. S., Nagamatsu, L. S., & Liu-Ambrose, T. (2017). Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. *Frontiers in Neuroendocrinology*, 46, 71–85. <https://www.sciencedirect.com/science/article/abs/pii/S0091302217300213?via%3Dihub>
- Eid, R. S., Gobinath, A. R., & Galea, L. A. M. (2019). Sex differences in depression: Insights from clinical and preclinical studies. *Progress in Neurobiology*, 176, 86–102. <https://www.sciencedirect.com/science/article/abs/pii/S030100821830087>

X?via%3Dihub

- Eissman, J. M., Dumitrescu, L., Mahoney, E. R., Smith, A. N., Mukherjee, S., Lee, M. L., Scollard, P., Choi, S. E., Bush, W. S., Engelman, C. D., Lu, Q., Fardo, D. W., Trittschuh, E. H., Mez, J., Kaczorowski, C. C., Hernandez Saucedo, H., Widaman, K. F., Buckley, R. F., Properzi, M. J., & Mormino, E. C. (2022). Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. *Oxford Academic*. <https://academic.oup.com/brain/article/145/7/2541/6585174>
- Emrani, S., Sunderman, E. (2025, April) Sex/gender differences in the clinical trajectory of Alzheimer's disease: Insights into diagnosis and cognitive reserve. *Science Direct*. <https://www.sciencedirect.com/science/article/pii/S009130222500010X#s0050>
- Iorga, A., Cunningham, C. M., Moazeni, S., Ruffenach, G., Umar, S., & Eghbali, M. (2017). The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biology of Sex Differences*, 8(1). <https://doi.org/10.1186/s13293-017-0152-8>
- Levine, D. A., Gross, A. L., Briceño, E. M., Tilton, N., Giordani, B. J., Sussman, J. B., Hayward, R. A., Burke, J. F., Hingtgen, S., Elkind, M. S. V., Manly, J. J., Gottesman, R. F., Gaskin, D. J., Sidney, S., Sacco, R. L., Tom, S. E., Wright, C. B., Yaffe, K., & Galecki, A. T. (2021). Sex Differences in Cognitive Decline Among US Adults. *JAMA Network Open*. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776902>
- Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., Josephs, K. A., Fang, P., Pandey, M. K., Murray, M. E., Kantarci, K., Jones, D. T., Vemuri, P., Graff-Radford, J., Schwarz, C. G., Machulda, M. M., Mielke, M. M., Roberts, R. O., Knopman, D. S., & Petersen, R. C. (2017). Widespread brain tau and its association with aging, Braak stage and Alzheimer's dementia. *Brain*, 141(1), 271–287. <https://pubmed.ncbi.nlm.nih.gov/29228201/>
- McDermott, K. L., G. Peggy McFall, Andrews, S. J., Anstey, K. J., & Dixon, R. A. (2016). Memory Resilience to Alzheimer's Genetic Risk: Sex Effects in Predictor Profiles. *Oxford Academic*. <https://academic.oup.com/psychsocgerontology/article/72/6/937/2740384>
- Morrison, C., Mahsa Dadar, & Collins, D. L. (2023). Sex differences in risk factors, burden, and outcomes of cerebrovascular disease in Alzheimer's disease populations. *Alzheimer S & Dementia*, 20(1), 34–46. <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13452>

Into the Quantum Era: Investigating Quantum Key Distribution's Role in Cybersecurity

Nishant Ambegaonkar

Abstract: Advances in quantum computing threaten the long-term security of classical cryptographic systems that rely on mathematical complexity and assumptions about limited computational power. As quantum algorithms become capable of breaking widely used encryption schemes, classical cryptography is increasingly

viewed as vulnerable, creating a need for more secure alternatives. This study examines how quantum key distribution (QKD) improves security compared to classical cryptography and evaluates whether it is viable for widespread implementation. Through a structured literature review, this paper analyzes three themes: the fundamental security differences between classical cryptography and QKD, the practical and theoretical limitations of QKD, and the latest developments aimed at improving its scalability and reliability. Research indicates that QKD provides stronger theoretical encryption by relying on quantum mechanical principles such as superposition and the no-cloning theorem, enabling the detection of eavesdropping and offering information-theoretic security. However, a multitude of challenges remain, including high infrastructure costs, limited transmission distances, hardware sensitivity, and the complexity of finite-size and composable security proofs. Overall, while QKD has the potential to replace classical key exchange in a post-quantum era, continued development of new technologies and expansion of infrastructure are necessary before it can be implemented on a global scale.

Keywords: Quantum Key Distribution, Classical Cryptography, Post Quantum Cryptography, Finite-Size Security, Composable Security, Information-Theoretic Security

Introduction

The need for secure encryption is growing as modern society becomes increasingly dependent on digital communication. Sensitive information such as financial transactions, medical records, and government communications relies on encryption to remain private and protected from unauthorized access. As technology advances, the security provided by traditional cryptographic systems is being challenged (Abudalou, 2024). In particular, the rapid development of both classical and quantum computing has prompted concerns about whether existing encryption methods will remain effective in the future.

Classical cryptographic methods secure data by relying on mathematical complexity, assuming that certain problems, such as factoring large numbers, are computationally expensive for attackers (Goldwasser, 2002). While these methods have been effective in the past, they are becoming more vulnerable as computational power increases. The emergence of quantum computers poses an especially serious threat, as quantum algorithms are capable of solving some of these mathematical problems far more efficiently than classical computers. As a result, cryptographic systems that are currently considered secure may become obsolete, emphasizing the critical necessity for stronger and more resilient encryption techniques.

Quantum cryptography offers a fundamentally different approach to securing communication. Rather than depending on mathematical difficulty, quantum cryptography is based on the laws of quantum mechanics. These principles allow security to be enforced by physical phenomena, such as the disturbance caused by measuring a quantum system. As a consequence, quantum cryptography has the potential to provide stronger guarantees against eavesdropping than classical methods, even in the presence of powerful attackers (Renner & Wolf, 2023).

One of the most prominent applications of quantum cryptography is quantum key distribution (QKD). QKD enables two parties to securely exchange encryption keys by encoding information in quantum states. Any attempt by a third party to intercept or measure

these states causes detectable disturbances to the system, alerting the communicating parties to the presence of an eavesdropper. This ability to detect interception gives QKD a major advantage over classical key exchange methods, which cannot inherently detect unauthorized access (Wolf, 2021).

Overall, this paper will explore quantum key distribution's potential to drastically improve cybersecurity in comparison to the level provided by classical cryptographic methods. It will also discuss the obstacles that remain before widespread implementation of QKD is possible.

QKD vs. Classical Cryptographic Methods

Classical cryptographic methods and QKD differ fundamentally in how they achieve security, and examining this contrast is crucial to understanding why QKD represents a major improvement in cybersecurity. Classical cryptography relies on mathematical complexity and the assumption that attackers have limited computational power. In contrast, QKD derives its security directly from the laws of quantum mechanics. This difference allows QKD to detect eavesdropping and theoretically provide unbreakable encryption, which classical cryptography is unable to accomplish. Exploring this theme supports the thesis by demonstrating why QKD offers a significant security advantage over classical cryptographic methods.

One major weakness of classical cryptography is its vulnerability to advances in quantum computing. Sahu and Mazumdar (2024) explain that widely used encryption schemes such as the Rivest-Shamir-Adelman algorithm and elliptic curve cryptography depend on certain mathematical problems, often factoring large numbers or solving complex logarithms, which can be efficiently solved using quantum algorithms. Particularly, Shor's algorithm is capable of breaking these systems by undermining the assumption of computational difficulty with which they rely (Shor, 2002). As a result, encrypted data protected by classical methods may become accessible to attackers once sufficiently powerful quantum computers exist.

Furthermore, Sahu and Mazumdar argue that QKD provides "unparalleled security" because it is based on quantum principles such as superposition and the no-cloning theorem, which make undetected eavesdropping theoretically impossible. Superposition allows a quantum particle, such as a photon, to exist in multiple states at the same time until it is measured. In QKD protocols such as BB84, which is the most common, information is encoded in quantum states that do not have definite values prior to measurement. When a legitimate receiver measures these states using the correct key, the intended information is recovered. However, if an eavesdropper attempts to intercept and measure quantum states, their measurement forces the system to collapse into a definite state, altering the original information.

For example, as Figure 1 illustrates, Alice prepares a quantum state and sends it through a quantum channel to Bob, who measures it to obtain a key bit. If an eavesdropper (Eve) attempts to intercept the state, they inevitably measure some states incorrectly because they do not know which key was used to encode each quantum state. These incorrect measurements disturb the quantum system. This results in an unusually high error rate which shows up in Bob's results, and alerts Alice and Bob of potential eavesdropping (Namkung & Kwon, 2024). Classical cryptographic methods cannot detect interception in this way.

Moreover, the no-cloning theorem strengthens QKD's resistance to eavesdropping by stating that it is impossible to create an exact copy of an unknown quantum state. This means an eavesdropper cannot duplicate the transmitted quantum information and then forward the original without detection. Any attempt to copy the quantum states necessarily alters them, again introducing observable disturbances (Sahu & Mazumdar, 2024). After comparing both QKD and classical cryptography, it is evident that QKD is fundamentally more secure than classical cryptographic methods in the quantum era.

To add on to this argument, Upadhyaya et al. (2021) demonstrates that QKD's security can be rigorously proven even in infinite-dimensional quantum systems. Classical cryptography depends on assumptions about attacker limitations, but the authors show that QKD can maintain information theoretic security regardless of an adversary's computational power. By introducing a dimension-reduction method that enables reliable numerical security analysis without artificial cutoff assumptions, this research preserves security in realistic implementations. This work reinforces the claim that QKD offers stronger long-term security guarantees than classical key-exchange methods, which are vulnerable to unforeseen technological breakthroughs.

Metger and Renner, (2023) further support QKD's superiority by using the generalized entropy accumulation theorem (GEAT), a framework that allows security to be analyzed across multiple rounds of a QKD protocol. In practice, QKD operates with a finite number of exchanged quantum signals. GEAT makes it possible to track how randomness, referred to as entropy, about the secret key accumulates over each round of the protocol, even after the most powerful attacks allowed by physics. From this theorem, the researchers were able to develop realistic security bounds without relying on unrealistic assumptions.

Furthermore, due to these realistic security bounds, the authors demonstrated that GEAT supports finite-size security, meaning that QKD can be proven secure by a limited number of exchanged quantum states, as opposed to infinite. Classical cryptographic proofs often depend on computational assumptions, but Metger and Renner have established that QKD security remains valid under realistic constraints. Their approach demonstrates that security against simpler attacks implies security against the most powerful attacks. This realization made their analysis more practical.

Lastly, Metger and Renner emphasize composable security. This means that a key generated through QKD remains secure when used in other cryptographic applications, such as encryption or authentication. Composable security guarantees that security does not degrade for real-world systems. By proving composable, finite-size security using GEAT, their work shows that QKD can ensure comprehensive, end-to-end security guarantees that classical cryptographic methods cannot match.

In all, these sources demonstrate that while classical cryptography is increasingly vulnerable to advances in computing power, QKD offers a fundamentally different and more secure approach to encryption. By relying on quantum mechanics rather than mathematical assumptions, QKD can detect eavesdropping and remaining secure even against unforeseen attacks, quantum or otherwise. This comparison supports the thesis that quantum key distribution has the potential to drastically improve cybersecurity, even though practical challenges still limit its extensive implementation.

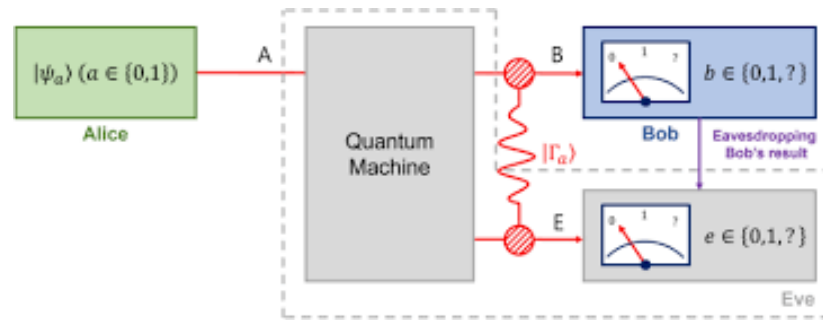


Figure 1. Quantum key distribution setup showing how when Alice (green) sends a quantum state (a) to Bob (blue) who receives quantum state (b), a mismatch to the key he was sent, indicated by (?). This incorrect result is induced by detectable disturbances (red zigzag) introduced by Eve (gray) during her attempts to intercept (Namkung & Kwon, 2024).

Limitations of QKD

Despite the strong theoretical security advantages of QKD, several limitations currently prevent its widespread implementation. Despite QKD's theoretical features due to its quantum mechanics base, it is still not always perfectly secure in real-world conditions. Examining the many limitations of QKD is essential to evaluating its feasibility as a large-scale replacement for classical cryptographic systems. These limitations directly support the thesis by demonstrating that significant obstacles must still be overcome before QKD can be broadly deployed.

One major conceptual limitation of QKD concerns how its security guarantees are defined and interpreted. Yuen (2016) examines common claims that QKD provides perfect or unbreakable security and argues that these claims are often overstated in real-life situations. They emphasize that QKD security is frequently evaluated using abstract mathematical metrics, such as trace distance, rather than operational measures like an attacker's probability of successfully guessing the key. This distinction is important because real-world security depends on how likely an adversary is to compromise the system, not just on theoretical bounds. This analysis shows that QKD can improve security compared to classical cryptography, yet its guarantees are more limited in practice than often assumed. This underscores a significant obstacle to widespread trust and adoption; QKD's security advantages only hold when its metrics are correctly used.

In addition to conceptual challenges, QKD encounters substantial practical implementation barriers. Sahu and Mazumdar (2024) explain that current QKD systems require specialized infrastructure such as single-photon sources, highly sensitive detectors, and low-noise transmission channels like fiber-optic cables. These systems are expensive, difficult to maintain, and often limited in transmission distance. Hardware imperfections and environmental noise can introduce errors that reduce key generation rates or compromise security if not managed properly. In contrast, classical cryptographic systems are relatively inexpensive, flexible, and easy to deploy using existing infrastructure. These cost and scalability issues represent a major obstacle to the widespread implementation of QKD, despite its theoretical security advantages.

Another limitation arises from the complexity of achieving strong security guarantees in realistic settings. Metger and Renner (2023) show that proving QKD security under real-world conditions requires advanced frameworks like GEAT. While this approach strengthens QKD by enabling finite-size and composable security proofs, it also introduces significant mathematical and

computational complexity. Finite-size security refers to proving security when only a limited number of quantum signals are exchanged, which reflects real systems rather than idealized infinite ones. Composable security ensures that a QKD-generated key remains secure when used within larger cryptographic protocols. Although these properties are essential for practical deployment, the difficulty of implementing and verifying such rigorous security models presents another obstacle to large-scale adoption.

Overall, these limitations demonstrate that while QKD offers fundamentally stronger security than classical cryptographic methods, it is not yet ready for widespread use. The combined challenges of misunderstandings, high costs, and the need for advanced technologies all hinder its practical deployment. This substantiates the notion that QKD's revolutionary potential in cybersecurity is accompanied by considerable challenges that must be addressed before it can become a mainstream solution.

How QKD is Being Improved

Although the limitations of quantum key distribution constitute formidable obstacles to widespread implementation, ongoing research demonstrates that many of these obstacles are not permanent. Rather than undermining QKD's potential, these challenges have motivated the development of stronger security proofs and scalable system designs. By addressing both the conceptual and technical weaknesses previously identified, researchers are working to close the gap between QKD's theoretical advantages and its real-world feasibility. These improvements reinforce the thesis by showing that while QKD is not yet universally deployable, it is steadily becoming more practical and reliable for future cybersecurity applications.

One major improvement involves strengthening QKD's security guarantees under realistic conditions. Metger and Renner (2023) introduced GEAT, which provides a systematic way to measure how uncertainty builds up across multiple rounds of a QKD protocol. In their work, entropy represents how much information an eavesdropper lacks about the final secret key. GEAT allows researchers to calculate secure key lengths even when only a finite number of quantum signals are exchanged, a concept known as finite-size security. This is significant because real-world systems cannot rely on idealized infinite key lengths. Their framework also ensures composable security, meaning that a QKD-generated key remains secure when used within other cryptographic protocols, such as encryption or authentication systems. By strengthening QKD's security in realistic, finite settings, this work directly addresses

concerns raised about overly idealized security assumptions.

In addition to stronger security proofs, improvements in computational methods are making QKD more practical. Upadhyaya et al. (2021) develop a dimension-reduction method that allows QKD protocols operating in infinite-dimensional Hilbert spaces to be analyzed more efficiently. A Hilbert space is the mathematical structure used to describe quantum states, and in many continuous-variable QKD systems, this space is theoretically infinite. Analyzing security in such systems can be computationally demanding. The authors' dimension-reduction approach maps these infinite-dimensional systems onto finite ones without sacrificing information-theoretic security (impenetrable cryptographic security given an attacker has infinite time and computational strength). This makes security verification more computationally feasible while preserving the fundamental security guarantees that distinguish QKD from classical cryptography. By reducing analytical complexity, this improvement supports scalability and practical deployment.

Protocol-level innovations also contribute to QKD's advancement. Primaatmaja et al. (2021) propose a hybrid QKD protocol that combines discrete-variable encoding with homodyne detection, a measurement technique commonly used in continuous-variable systems. One key improvement is the elimination of a shared phase reference between communicating parties, which simplifies system configuration and reduces implementation challenges. By maintaining strong security guarantees while increasing practicality and transmission feasibility over metropolitan-scale distances, this hybrid approach demonstrates how engineering improvements can enhance scalability. Such developments show that QKD is evolving beyond purely theoretical models toward adaptable and deployable systems.

Together, these advancements indicate that the obstacles facing QKD are actively being addressed through theoretical refinement and technological innovation. While challenges related to infrastructure, cost, and complexity remain, improvements in security frameworks and design are steadily increasing QKD's practicality. These developments support the thesis by demonstrating that although widespread implementation is not yet achievable, quantum key distribution is progressing toward becoming a viable long-term solution for secure global communication.

Conclusion

The rapid advancement of quantum computing poses a direct threat to existing classical encryption systems that secure global and digital communication. Quantum key distribution has the potential to drastically improve cybersecurity in comparison to the level provided by classical cryptographic methods, but there are still many obstacles that remain before widespread use of it is possible. While QKD offers fundamentally stronger security guarantees by relying on quantum mechanics rather than computational assumptions, its widespread adoption remains constrained by real-world limitations.

The comparison between QKD and classical cryptography demonstrates why QKD is viewed as a transformative development in secure communication. Classical cryptographic methods rely on mathematical complexity and assumptions about limited computational power and thus, are vulnerable to quantum attacks. In contrast, QKD provides fool-proof security based on quantum mechanics, making it fundamentally more secure against future threats to cybersecurity. Although QKD offers theoretically impenetrable

security, it faces practical limitations such as high implementation costs, limited transmission distances, and sensitivity to real-world noise and hardware imperfections. These challenges currently restrict widespread adoption and highlight the gap between theoretical security and practical deployment. At the same time, recent research shows that QKD can be improved through advances in security proofs, hybrid protocols, and techniques that address finite-size effects and realistic system constraints. These improvements increase practicality and scalability, allowing for QKD to become close to large-scale implementation across the world.

It is important to note that this literature review is limited by its reliance on theoretical analyses and emerging research rather than large-scale implementation data. Many of the security guarantees discussed are based on controlled or idealized conditions, and infrastructure required for widespread QKD deployment remains underdeveloped. These limitations expose the need for further experimental validation and technological advancement along with increased funding and attention towards QKD research before it can fully replace classical cryptographic systems.

Overall, as quantum technologies continue to develop, the reliability of current cryptographic infrastructure becomes increasingly uncertain. Evaluating the strengths and weaknesses of QKD is therefore essential for determining whether it can serve as a long-term solution for cybersecurity in the future.

References

- Abudalou, M. (2024). Enhancing data security through advanced cryptographic techniques. *Int. J. Comput. Sci. Mob. Comput.*, 13(1), 88-92.
- Goldwasser, S. (2002). Mathematical foundations of modern cryptography: computational complexity perspective. *arXiv preprint cs/0212055*.
- Metger, T., & Renner, R. (2023). Security of quantum key distribution from generalised entropy accumulation. *Nature Communications*, 14(1), 5272.
- Namkung, M., & Kwon, Y. (2024). Analysis of quantum key distribution based on unified model of sequential state discrimination strategy. *Scientific Reports*, 14(1), 10254.
- Primaatmaja, I. W., Liang, C. C., Zhang, G., Haw, J. Y., Wang, C., & Lim, C. C. W. (2022). Discrete-variable quantum key distribution with homodyne detection. *Quantum*, 6, 613.
- Renner, R., & Wolf, R. (2023). Quantum advantage in cryptography. *AIAA journal*, 61(5), 1895-1910.
- Sahu, S. K., & Mazumdar, K. (2024). State-of-the-art analysis of quantum cryptography: applications and future prospects. *Frontiers in physics*, 12, 1456491.
- Shor, P. W. (2002, May). Introduction to quantum algorithms. In *Proceedings of symposia in applied mathematics* (Vol. 58, pp. 143-160).
- Upadhyaya, T., Van Himbeeck, T., Lin, J., & Lütkenhaus, N. (2021). Dimension reduction in quantum key distribution for continuous-and discrete-variable protocols. *PRX Quantum*, 2(2), 020325.
- Wolf, R. (2021). *Quantum key distribution* (Vol. 988). Berlin/Heidelberg, Germany: Springer

International Publishing.

Yuen, H. P. (2016). Security of quantum key distribution. *IEEE Access*, 4, 724-749.

Alzheimer's Disease Diagnostic Methods: Techniques, Limitations, and Future Directions

Kolbi Herzfeld

Abstract: Alzheimer's disease is a progressive neurodegenerative disorder affecting millions of people worldwide, with cases expected to rise significantly in the coming decades. Early detection is critical because current treatments are most effective before extensive neuronal damage occurs; however, most diagnoses happen after symptoms appear, limiting positive impact. This paper examines current diagnostic methods for Alzheimer's disease, evaluates their limitations, and explores emerging approaches aimed at improving early detection. This study is based on an analysis of existing review and research articles on Alzheimer's diagnostics. Existing methods include neuroimaging (MRI, PET, CT, SPECT), genetic testing, biomarker analysis of blood and cerebrospinal fluid, and cognitive assessments. While these methods can support diagnosis they are often expensive, invasive, and insufficiently sensitive for detecting the disease in its preclinical stages. Additionally, many biomarkers lack standardized thresholds, and diagnostic accuracy frequently depends on combining multiple modalities. Emerging diagnostic strategies, including salivary biomarkers, retinal imaging, and artificial intelligence based speech analysis, offer promising, less invasive alternatives with potential for earlier detection. However, these methods remain under investigation and require further validation in larger, diverse populations. Overall, this paper highlights an important gap between current diagnostic capabilities and the need for early identification of Alzheimer's disease, and will elucidate the future of Alzheimer's diagnostics and treatment. Future research should focus on improving accessibility, standardization, and integration of diagnostic tools to enable earlier intervention and improve patient outcomes.

Keywords: Alzheimer's disease, early detection, biomarkers, neuroimaging, genetic testing, cognitive tests, diagnosis, saliva, retinal imaging, artificial intelligence

Alzheimer's disease is a progressive neurodegenerative disorder that affects 7 million Americans today, and this number is projected to grow to 13.8 million by 2060.¹ The current estimated burden for caregivers treating family members with Alzheimer's disease is a growing \$413 billion.¹ Added to that is the cost of medical care, treatments, and long-term care such as memory care facilities, aides, nurses, and social work services. Alzheimer's disease is the most common form of dementia and primarily affects the medial temporal lobe and neocortical structures as a result of the accumulation of two proteins, namely amyloid beta and tau.³ Amyloid beta deposition causes senile plaques in the hippocampus, the brain region that regulates learning and memory.³ Hyperphosphorylated forms of tau protein create neurofibrillary tangles that also drive neurodegeneration and cognitive dysfunction.³ This neurotoxicity results in brain atrophy and subsequent cognitive decline.

Amyloid beta and tau aggregation generally correspond to disease stage and severity.³ There are four clinical stages of Alzheimer's disease. The first is pre-clinical and can last for several years, featuring mild cognitive impairment and subtle changes in the hippocampus and cortex that frequently go unnoticed. There are no signs of functional impairment in daily activities in this phase. The early stage of Alzheimer's shows more behavioral symptoms and trouble with daily life. This is typically when patients present to the clinic and receive a diagnosis. Moderate Alzheimer's is where the plaques and tangles spread into the cerebral cortex areas, resulting in increased memory loss and dependency on caregivers. Late-stage Alzheimer's results in spread to the entire cortex area with severe memory loss and functional impairment, ultimately leading to death.³

Historically, Alzheimer's has only been diagnosed with 100% accuracy by postmortem autopsy, confirming the presence of amyloid plaques and tau tangles using histopathological methods.³ The field has progressed such that patients can receive a near-definitive diagnosis using a battery of diagnostic measures. These measures for a living patient include medical history, cognitive testing, genetic testing, biomarker analysis of blood and cerebrospinal fluid, and advanced imaging techniques, including PET, MRI, and CT scans.¹¹ Other methods under experimental usage are saliva, voice analysis, and ophthalmologic testing.

If new techniques can detect the disease early enough in the preclinical stage, before the visible irreversible damage has occurred to the brain, there is a chance to focus on therapeutics to stop the disease and help patients.¹⁰ However, the diagnostic tests used today still can not accurately diagnose someone in their pre-clinical stage.¹⁰ The availability of treatment for patients in the preclinical stage is lacking. The diagnostic modalities are not widely available to everyone, due to a combination of cost and awareness, and therefore, cumulative data on current methods are restricted.

There are currently no effective treatments for Alzheimer's patients that will reverse or stop the damage.¹⁰ While there are Alzheimer's medications approved by the FDA that target amyloid beta, Alzheimer's patients treated with these drugs continue to progressively lose cognitive function and quality of life.¹⁰ Earlier detection is necessary because patients are typically diagnosed too late in the disease stages to be adequately treated with medication.¹⁰ Any future treatments will be much more effective if they are applied to earlier diagnosed patients. The purpose of this paper is to discuss the current methods of detecting Alzheimer's and why new approaches are necessary. We will explore the limitations that inhibit testing accuracy, and new promising methods being developed. By delineating where research and techniques are currently stationed, and what steps are being taken to improve said techniques, we may gain a better understanding of the disease and improve future patient outcomes.

Diagnostic Methods

Imaging

Diagnostic imaging for Alzheimer's includes a combination of CT, MRI, PET, and SPECT.¹¹ CT scans obtain images of the brain using ionizing radiation. CT scans are not used to identify Alzheimer's, but rather to rule out other causes of cognitive impairment (tumors, stroke, hydrocephalus, etc).¹¹ Structural MRI scans track volume changes in the brain. The hallmark MRI finding

in Alzheimer's patients is brain atrophy in the hippocampus, entorhinal cortex, and temporal lobe.¹¹ Structural MRI scans also help differentiate between AD and other types of dementia.¹¹ It can be used to track disease progression, response to treatment, biomarker identification, and serve as a reference point for individuals at risk of developing Alzheimer's.¹¹ Functional MRI (fMRI) visualizes reduced brain activity between the default mode network and other brain regions.¹¹ fMRI can also be used to observe task-based activation patterns, which are reduced in Alzheimer's.¹¹ Another finding seen on fMRI in diseased patients is compensatory increased activation in regions involving attentional control.¹¹ Proton magnetic resonance spectroscopy (MRS) measures the levels of metabolites in specific brain regions.¹¹ In Alzheimer's, MRS displays increased levels of acetylcholine metabolites in the temporal and frontal lobes, and reduced levels of N-acetyl aspartate (NAA) due to reduction of neuronal integrity.¹¹ Alzheimer's imaging studies also show reduced glucose and cerebral lactate levels in MRS.¹¹ Proton magnetic resonance spectroscopy can monitor disease progression and treatment efficacy, allowing for early detection of disease progression.¹¹ PET scans use radiolabelled markers to provide information about brain metabolism, blood flow, and receptor sites for biomarkers.¹¹ Fluorodeoxyglucose (FDG) PET indicates activity at synapses using the FDG tracer. FDG PET shows reduced metabolism in the classic Alzheimer's disease brain sites, including the parietal, temporal, and hippocampus regions.¹¹ Beta-amyloid PET specifically identifies beta-amyloid plaques in the brain, allowing for the early detection of Alzheimer's even without symptoms.⁴ Pharmaceutical development of specific PET tracers that target beta amyloid, as well as tau and neurofibrillary tangles, substantially enhances this modality in both diagnosing AD and determining the efficacy of treatment.⁴ PET scan with tracers is considered the optimal neuroimaging technique for the diagnosis of Alzheimer's.⁴ SPECT is another imaging tool that follows brain changes in function and perfusion.⁷ SPECT helps differentiate AD from other dementias by identifying patterns in regional blood flow and metabolism, with characteristic reduced activity in the posterior cingulate cortex. SPECT scans can also be used to determine progression and response to treatment.⁷

Genetic testing

Genetic testing provides three purposes in Alzheimer's patients: Predictability, susceptibility, and medication decision-making.⁶ Testing for APP, PSEN1, and PSEN2 can predict Alzheimer's in asymptomatic patients with a family history of early-onset Alzheimer's. APOE genotyping can determine the likelihood or risk of Alzheimer's.⁶ APOE4 carriers are found in 40-65% of those with a diagnosis of Alzheimer's. Medication decisions have recently been relying on APOE status when considering the use of amyloid antibody therapy.⁶

Biomarkers

Biomarkers are measurable indicators found in blood and fluid that are used to display a disease state. The presence of certain plasma biomarkers improves diagnostic accuracy for AD.⁸ A low plasma amyloid-beta 42 to amyloid-beta 40 ratio can correlate with the earliest stages of Alzheimer's.⁸ Beta amyloid aggregates to form amyloid plaques. Of the isoforms of beta amyloid, beta amyloid 40 and 42 are considered the most significant in forming amyloid pathology. Beta amyloid 42 has a higher propensity to aggregate in the plaque, and therefore decreased levels in the blood correlate

with an increased number of amyloid plaques. Hence, the lower ratio is indicative of Alzheimer's pathology. Beta amyloid also promotes tau aggregation and phosphorylation and the development of tangles. Therefore, plasma tau levels directly demonstrate amyloid activity. Plasma total tau levels, t-tau, are associated with declines in cognitive function and can serve as a valuable predictor for the risk of cognitive decline.⁸ Higher levels of plasma phosphorylated tau (p-tau) have been found in patients with AD, and p-tau can also help distinguish Alzheimer's from other types of dementia.⁸ P-tau 181 and p-tau 217 demonstrate higher accuracy in distinguishing Alzheimer's from other dementias. Other weaker markers include neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). The combination of all these biomarkers can significantly improve diagnostic accuracy for AD.

Cerebrospinal fluid biomarkers of amyloid beta are also valuable for the early detection of Alzheimer's.⁵ A decrease in CSF levels of the amyloid beta peptide occurs before the appearance of amyloid plaques on imaging scans, making it a better candidate for earlier detection.⁵ Studies have also recommended using elevated levels of CSF t-tau in patients with AD and CSF p-tau as a more specific indicator for diagnosing AD.⁵

Neurological Exams

Neurological exams consist of a variety of tests that explore cognitive function. Basic neurologic history and physical exams look for aphasia, apraxia, gait disorders, and other pathologies that could support an AD diagnosis or indicate another process. Alzheimer's disease is characterized by difficulties with memory and behavior. Physicians may refer suspected Alzheimer's patients for a neuropsychological exam. Standard exams focus on attention, processing speed, memory, language, and executive functioning. Patients with AD commonly show impairments in verbal fluency and naming objects. Alzheimer's patients also have difficulty understanding new information and impaired recognition. Depression and dementia share similar characteristics, so neuropsychological exams help rule out either diagnosis.¹⁴ Doctors complete the Mini-Mental Status Exam (MMSE) or MOCA to screen a patient for cognitive dysfunction. Patients who fail the MMSE or MOCA are then sent for imaging and serology, as above.

Limitations

Imaging

Structural imaging for Alzheimer's provides extremely limited and non-specific information, making it less than ideal for diagnostic purposes.¹¹ CT scans show ultrastructural changes like brain atrophy and stroke, but do not label the toxic protein deposition associated with Alzheimer's. It is not recommended for routine assessment of Alzheimer's because it can only detect cortical atrophy. Medial temporal lobe atrophy is considered the marker of AD, and it is difficult to see that early on a CT scan, which is inferior in distinguishing gray and white matter. CT is also limited for soft tissue delineation and can miss the first signs of atrophy seen in the hippocampi. Although structural MRI scans can detect atrophy, they do not show the specific pathological hallmarks of Alzheimer's disease in the brain.¹¹ Structural MRI also does not assess function. Functional MRI has multiple problems in diagnosing Alzheimer's. The scan is extremely sensitive to head motion, which compromises the technique. If a patient can not adequately perform a task, the validity of the study is

compromised. It also requires long-term tracking of the patient and is not readily available for even insured patients as a covered test. Functional MRI is better used for research applications than diagnostic applications. While FDG PET scans can detect cellular metabolic changes that may indicate neurodegeneration, they are expensive and have limited availability.⁴ FDG PET involves an IV and exposure to radiation, thus exposing the patient. More importantly, FDG PET measures glucose uptake, which can be affected by various neurological disorders, not just Alzheimer's disease.⁴ Finally, amyloid PET scans are considered one of the gold standards of diagnosis, but are limited by their cost and availability.¹¹ They are not a good marker of progression because the degree of amyloid deposition doesn't necessarily correlate with cognitive decline.⁴ There are also no specific quantitative measures of amyloid, and radiologic observations broadly label a positive scan as "moderate to frequent" plaques. It is also not clear what level of amyloid deposition the PET scan is sensitive to, thus making it difficult for use in early-stage diagnosis.¹¹ SPECT scan performance is extremely variable depending on different tracers, equipment, and confirmation methods.⁷ It has a lower sensitivity and specificity for Alzheimer's compared to PET scans.⁷ SPECT can differentiate Alzheimer's from other forms of dementia due to variance in regional blood flow, but alterations to blood flow in the hippocampus are not exclusive to Alzheimer's disease and could be associated with other pathologies.⁷ SPECT scans are also not readily available or affordable. SPECT scans currently have more value in investigational settings than practical clinical settings.⁷ Taken together, imaging modalities serve less function as diagnostic tools and more as observational tools that can be used to better understand the disease.

Genetic Testing

Genetic testing for Alzheimer's disease can be problematic. Testing for the familial Alzheimer's associated genes, including APP, PSEN1, PSEN2, and APOE, can indicate genetic risk; however, heritable mutations only account for about 10% - 15% of Alzheimer's cases.⁶ Hence, a negative result in genetic testing does not ensure a negative diagnosis. Conversely, a positive APOE4/E4 profile does not guarantee an Alzheimer's diagnosis; it suggests susceptibility.⁶ PSEN1 and PSEN2 testing are typically reserved for patients with a family history of early-onset Alzheimer's, and are recommended to be done with a genetic counselor, given the psychological and clinical implications.⁶ Thus, genetic testing can predict and detect only a small fraction of Alzheimer's cases, and is not best suited for the average patient.

Biomarkers

Plasma biomarkers have emerged as a standard diagnostic modality in Alzheimer's. While low 42/40 amyloid ratios can correlate with early-stage Alzheimer's disease, longitudinal analysis of patients with Alzheimer's disease reveals that the amyloid beta 42/40 ratio is a less reliable measurement of brain beta amyloid than originally suspected.⁸ Amyloid beta exists in very low concentrations in blood compared to CSF, thus making it more difficult to detect in plasma-based biomarker assays.⁸ In addition, blood-based biomarker testing for A β 42/40 is not specific for brain amyloid, making it unreliable.¹³ P-tau181 and p-tau217 are considered more reliable biomarkers that increase with disease severity; however, to date, of the insurers, only Medicare covers the cost of this test, making it inaccessible for many patients.⁸ P-tau biomarkers are more reliable

for their negative predictive value. NfL and GFAP biomarkers are not specific for Alzheimer's, though they have some value in all-cause dementias and can support a diagnosis.⁸

CSF biomarkers require administering an invasive and painful lumbar puncture, which is unpopular among patients.⁵ CSF biomarkers are also not direct measures of plaques or tangles, meaning they do not quantify the amount of plaque in the brain.⁵ In blood, p-tau levels are far superior in detecting Alzheimer's compared to the beta 42/40 ratio.⁸ Tau levels in CSF can be increased by stroke, traumatic brain injury, and encephalitis, also making high pTau levels less reliable for the specific diagnosis of Alzheimer's.⁵ Additionally, by the time CSF tests are positive for pTau, significant neurological damage has already occurred.⁵

For all biomarker assays, the cutoff values for positive or negative diagnosis are still being determined, and are not sensitive enough to detect pTau or Amyloid Beta before patients present with symptoms, thus delaying diagnosis.¹¹

Neurological exams

Neuropsychological tests have multiple pitfalls when it comes to diagnosing a patient with Alzheimer's. Some researchers and clinicians argue that the test's ability to capture daily functioning and real-world data makes it a valid tool.¹⁴ The initial test is also done in real time and does not have any comparison to the specific patient's past performance and abilities. Cognitive testing is usually compared to national averages of other patients that are of a similar demographic with age, sex, ethnicity, and education level, but these comparisons may not capture individual changes to cognition.¹⁴ Initial cognitive testing is better used as a reference point or baseline to be compared to in the future. Additionally, it does not adequately distinguish between Alzheimer's and other cortical dementias.

Current models for accurate diagnosis of Alzheimer's involve multidimensional modalities using a combination of tests to reach a conclusion. Having to combine multiple methods to reach a potential diagnosis is inefficient and reduces the probability of earlier detection.¹⁰ While ongoing efforts are being made to improve each of the current assays to enhance sensitivity and reliability, new diagnostic assays are emerging that may provide alternate strategies for the diagnosis of Alzheimer's disease.

Emerging Diagnostic Modalities

Saliva

Similar biomarker patterns of Beta-amyloid 42 and p-tau were found in the saliva of Alzheimer's patients.² Beta-amyloid 42 and p-tau levels were increased in affected patients compared to age-matched controls, while salivary lactoferrin and t-tau were decreased.² Additionally, elevation of the enzyme acetylcholinesterase, a target of common current Alzheimer's treatments, was also noted in salivary samples of patients with Alzheimer's disease, suggesting it may be an important indicator of early disease.² While a salivary test presents a novel, minimally invasive, and stable option in comparison to lumbar punctures and blood, more research needs to be done to ascertain at what point the earliest detection is possible. Should it be an early phenomenon, salivary screening would be an ideal detection method in asymptomatic patients, potentially giving clinicians the ability to intervene in advance of symptom onset.²

Retinal Imaging

Alzheimer's specifically affects visuospatial function as a consequence of degeneration of optic nerves and retinal microvasculature. Optical coherence tomography angiography (OCTA) allows clinicians to acquire non-invasive images of the retinal microvasculature.⁹ While this method was initially developed to address ocular diseases, retinal microvascular imaging has been shown to distinguish between Alzheimer's and healthy patients, where patients with Alzheimer's have lower macular vascular density compared to controls.⁹ This non-invasive method could potentially serve as a prime strategy for diagnosing Alzheimer's, however there is not enough raw data yet to establish consistent diagnostic accuracy.⁹ It is important to note one limitation in this study is that it failed to use age-matched controls, and thus cannot distinguish age-related macular degeneration from Alzheimer's related changes in retinal microvasculature.

Speech

There are characteristic changes in speech patterns seen in Alzheimer's patients. Speech and language changes seen in this population include diminished lexical diversity and syntactic complexity.¹² One method being investigated as a diagnostic tool is to use machine-learning analysis of digital voice samples.¹² There are several artificial intelligence models working to distinguish Alzheimer's from non-Alzheimer's linguistic patterns, however these models require more training to sensitively distinguish the two.¹² Alzheimer's patients consistently performed poorer in naming and language informativeness. Advanced machine learning models are able to successfully separate mild cognitive impairment, Alzheimer's, and non Alzheimer's dementias within 95% confidence intervals.¹² With the expansion of artificial intelligence and machine learning, the expectation is that this can become a valuable early tool for diagnosis.¹²

Conclusion

Alzheimer's disease affects millions of people and, with emerging anti-amyloid therapy, will be most effectively treated when it is detected as early as possible, yet current diagnostic methods often identify the disease only after substantial neurological damage has already occurred. Earlier detection of Alzheimer's is essential for improving treatment outcomes, slowing cognitive decline, and giving patients more time for intervention and planning. Although existing tools such as imaging, genetic testing, biomarkers, and neurological exams have improved clinicians' ability to diagnose Alzheimer's, they are still limited in sensitivity, accessibility, and usefulness during the earliest stages of disease progression.

Current diagnostic methods each contribute important information, but none is sufficient on its own. Imaging tools such as MRI, PET, CT, and SPECT can reveal structural, metabolic, and pathological changes in the brain, while blood and cerebrospinal fluid biomarkers can detect amyloid beta and tau abnormalities associated with Alzheimer's pathology. Genetic testing, especially APOE genotyping and APP, PSEN1, and PSEN2 mutation screening, can identify risk or predict rare familial forms of the disease. Cognitive and neurological exams such as the MMSE and MoCA also remain useful for identifying functional impairment. However, these methods are often expensive, invasive, unavailable to many patients, or better suited to confirm disease rather than detecting it at the earliest possible point.

These limitations cause delayed diagnosis, which reduces the opportunity for meaningful treatment. By the time many patients present with memory loss or impaired functioning, the underlying disease process has been developing for years. This makes the search for new diagnostic methods especially important. Emerging approaches such as salivary biomarkers, retinal imaging, and machine-learning analysis of speech patterns may offer less invasive, more accessible, and potentially earlier ways to identify Alzheimer's disease. While these methods are still under investigation, they represent an important shift toward screening tools that could be used before severe symptoms appear.

At the same time, this research has several limitations. Many of the newer studies rely on small sample sizes, limited long-term data, and populations that may not represent the full diversity of patients affected by Alzheimer's disease. No single method currently provides a completely definitive early diagnosis, and some biomarkers still lack clearly established cutoff values across populations. Future research should focus on testing these methods in larger and more diverse groups, improving affordability and accessibility, and combining multiple diagnostic strategies to increase accuracy. Overall, the evidence suggests that the future of Alzheimer's will not depend on one perfect test, but on the development of earlier, more practical, and more inclusive approaches to detection.

References

1. Alzheimer's Association. (2024). 2024 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 20(5), 3708–3821. <https://doi.org/10.1002/alz.13809>
2. Ashraf, M., Sheikh, I. & Ashraf, M. Salivary biomarkers in Alzheimer's. *Br Dent J* 239, 231–232 (2025). <https://doi.org/10.1038/s41415-025-9130-4>
3. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106.
4. Chapleau, M., Iaccarino, L., Soleimani-Meigooni, D., & Rabinovici, G. D. (2022). The role of amyloid PET in imaging neurodegenerative disorders: A review. *Journal of Nuclear Medicine*, 63(Suppl 1), 13S–19S. <https://doi.org/10.2967/jnumed.121.263195>
5. de Leeuw DM, Trieu C, Vromen EM, et al. Cerebrospinal Fluid Amyloid and Tau Biomarker Changes Across the Alzheimer Disease Clinical Spectrum. *JAMA Netw Open*. 2025;8(7):e2519919. doi:10.1001/jamanetworkopen.2025.19919
6. de Rojas, I., Hulsman, M., Tesi, N. et al. Genetic testing of common and rare variants in dementia patients from a memory clinic. *Alz Res Therapy* 17, 225 (2025). <https://doi.org/10.1186/s13195-025-01854-z>
7. Ferrando R and Damian A (2021) Brain SPECT as a Biomarker of Neurodegeneration in Dementia in the Era of Molecular Imaging: Still a Valid Option?. *Front. Neurol.* 12:629442. doi: 10.3389/fneur.2021.629442
8. Grande, G., Valletta, M., Rizzuto, D. et al. Blood-based biomarkers of Alzheimer's disease and incident dementia in the community. *Nat Med* 31, 2027–2035 (2025). <https://doi.org/10.1038/s41591-025-03605-x>
9. Heydari, K., Enichen, E.J., Wang, S. et al. A novel model for

- retinal imaging in the diagnosis of Alzheimer's disease. *npj Digit. Med.* 8, 19 (2025). <https://doi.org/10.1038/s41746-025-01437-09>
10. Pais, M., Martinez, L., Ribeiro, O., et al. (2020). Early diagnosis and treatment of Alzheimer's disease: New definitions and challenges. *Brazilian Journal of Psychiatry*, 42(4), 431–441. <https://doi.org/10.1590/1516-4446-2019-0735>
 11. Leuzy A, Bollack A, Pellegrino D, et al. Considerations in the clinical use of amyloid PET and CSF biomarkers for Alzheimer's disease. *Alzheimer's Dement.* 2025;21:e14528. <https://doi.org/10.1002/alz.14528>
 12. Mulumba J, Duan R, Luo B, Wu J, Sulaiman M, Wang F, et al. The role of neuroimaging in Alzheimer's disease: implications for the diagnosis, monitoring disease progression, and treatment. *Explor Neurosci.* 2025;4:100675. <https://doi.org/10.37349/en.2025.100675>
 13. Rezaii, N., Wong, B., Aisen, P. et al. Voiceprints of cognitive impairment: analyzing digital voice for early detection of Alzheimer's and related dementias. *npj Dement.* 1, 35 (2025). <https://doi.org/10.1038/s44400-025-00040-0>
 14. Pasi, M., Poggesi, A., & Pantoni, L. (2011). The use of CT in dementia. *International Psychogeriatrics*, 23(S2), S6–S12. <http://doi.org/10.1017/S1041610211000950>
 15. Wegierek AMJ, Lesniak K, Patel S, et al. A Collaborative Approach to Treatment of Alzheimer's Disease from a Psychological Perspective. In: Wisniewski T, editor. *Alzheimer's Disease* [Internet]. Brisbane (AU): Codon Publications; 2019 Dec 20. Chapter 15. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK552143/doi/10.15586/alzheimersdisease.2019.ch15>

Moderate-to-Severe Psoriasis: Advancing Skin Clearance through Novel Biologic Therapy

Scarlett Brez

Abstract: Psoriasis is a chronic inflammatory disease characterized by accelerated skin cell production and the formation of scaly plaques that significantly affect physical health and psychological well-being. Moderate-to-severe cases often require systemic treatment to control disease progression and improve patient outcomes. In just the past few years, newly developed biologic therapies that target specific immune pathways have rapidly transformed psoriasis management in moderate-to-severe adults by directly inhibiting inflammatory signals responsible for disease progression. Clinical evidence demonstrates that biologics achieve significantly higher rates of skin clearance compared with traditional systemic treatments, such as methotrexate. These therapies frequently lead to near-complete disease clearance, whereas non-biologic therapies typically result in more moderate improvement. Despite their efficacy and generally favorable safety profiles when properly monitored, access to biologic therapies may be limited by high costs, insurance requirements, and disparities in healthcare. Improved skin clearance is also strongly associated with enhanced quality-of-life outcomes, including reductions in itching, physical discomfort, psychological distress, and social stigma. This paper

examines the differences between biologic and traditional systemic treatments for adults with moderate-to-severe psoriasis, focusing on mechanisms of action, clinical efficacy, and quality-of-life outcomes. Overall, biologic therapies provide more targeted immune modulation and sustained disease control, leading to greater improvements in clinical outcomes and patient quality of life for individuals with moderate-to-severe psoriasis.

Keywords: Psoriasis; biologic therapy; systemic therapy; PASI clearance; quality of life

Background

Psoriasis is a chronic autoimmune disorder characterized by immune-mediated inflammation that accelerates keratinocyte proliferation, leading to erythematous, scaly plaques (Feng & Liao, 2025). Symptoms include itching, burning, flaring, and physical discomfort (Armstrong & Read, 2020). Beyond physical manifestations, psoriasis is also associated with severe psychological burden, including social stigma, impaired quality of life, anxiety, and depression (Strober et al., 2019). Moderate-to-severe psoriasis is defined by greater body surface area (BSA) involvement, higher lesion severity, and substantial impact on quality of life (Strober et al., 2024). Moderate psoriasis typically involves 3 to 10 percent BSA or significant involvement of functionally or socially sensitive areas, such as the face, hands, or genitals. Severe psoriasis involves greater than 10 percent BSA, extensive plaque thickness and erythema, or marked impairment in daily functioning, generally requiring systemic or biologic treatment (Strober et al., 2024). While there is currently no cure, treatment options are constantly evolving to better manage both the physical and emotional burdens of the disease. Psoriasis treatments aim to reduce inflammation, slow skin cell turnover, and improve quality of life (Chan, 2025). Current treatment options for psoriasis include topical therapies, phototherapy, systemic agents (including methotrexate and cyclosporine), targeted biologic therapies (including TNF- α , IL-17, or IL-23 inhibitors), and newer oral small-molecule agents (such as PDE4 and TYK2 inhibitors) (Chan, 2025). Treatment selection depends on disease severity, affected areas, responses to prior therapy, and patient preference.

In recent years, biologic therapies have significantly changed the management of moderate-to-severe psoriasis. The pathogenesis of psoriasis is driven by dysregulated immune signaling in which pro-inflammatory cytokines activate immune cells and stimulate keratinocyte proliferation, resulting in the formation of characteristic erythematous, scaly plaques. Cytokines such as tumor necrosis factor (TNF), interleukin-17 (IL-17), and interleukin-23 (IL-23) play central roles in sustaining this inflammatory cascade and promoting excessive keratinocyte growth within the epidermis. Biologic therapies are medications derived from living cells that selectively target specific cytokines or immune mediators involved in this inflammatory pathway, thereby interrupting the signals that drive chronic skin inflammation and abnormal keratinocyte activity. Unlike systemic anti-inflammatory medications that broadly suppress immune activity, biologics precisely inhibit discrete molecular pathways responsible for disease progression, allowing for targeted modulation of the immune response while minimizing widespread immunosuppression (Liang et al., 2026).

Treatment outcomes in psoriasis are typically evaluated using measures such as skin clearance rates, quality-of-life indicators, and reductions in flare frequency. Skin clearance rates assess the

degree to which plaques improve or resolve, often measured using standardized tools such as the Psoriasis Area and Severity Index (PASI) (West, 2025). The PASI evaluates four body regions (head, upper limbs, trunk, and lower limbs) based on erythema (redness), induration (thickening), scaling, and the percentage of body surface area involved. Treatment response is commonly expressed as percentage improvement from baseline evaluation, such as PASI 75 or PASI 90, which represent 75% and 90% clearance of disease (West, 2025). These two measures are most commonly used in psoriasis research, as they provide standardized and clinically meaningful thresholds for comparing treatment effectiveness across studies (Novartis, n.d). Quality-of-life indicators assess how psoriasis affects daily functioning, emotional well-being, social relationships, patient satisfaction, and overall mental health. Reducing the frequency and severity of flares is also essential, as persistent or recurring symptoms can worsen both physical discomfort and psychological distress. Targeted inhibition of the IL-17 and IL-23 pathways enables more consistent suppression of the inflammatory cascade driving keratinocyte proliferation, resulting in sustained plaque resolution and reduced flare frequency (Liang et al., 2026). This targeted immune modulation can also alleviate many of the physical manifestations of psoriasis, including erythema, scaling, skin thickening, and persistent pruritus, which often contribute to discomfort, irritation, and visible skin lesions. As plaques diminish and inflammation subsides, patients frequently experience reduced skin pain, decreased cracking or bleeding of lesions, and improved skin texture and appearance. Greater levels of disease control are also associated with improvements in pruritus, daily functioning, and psychosocial well-being. These findings highlight the improved and sustained therapeutic impact of newer targeted agents compared to traditional non-biologic treatments, as clinical evidence demonstrates meaningful differences in the degree and durability of disease control achieved between biologic therapies and conventional non-biologic treatments.

Therefore, in adults with moderate-to-severe psoriasis, biologic therapy offers superior improvements in skin clearance and quality of life compared to non-biologic treatment options due to its targeted mechanism of action and sustained control of inflammatory pathways. This paper will analyze the mechanistic, clinical, and quality-of-life benefits of biologic therapies in comparison to traditional non-biologic treatment options.

Psoriasis: Clinical Manifestations and Inflammatory Response

Psoriasis develops from a complex interplay between genetic susceptibility and immune dysregulation that sustains chronic inflammation in the skin (Feng & Liao, 2025). Activation of inflammatory pathways, including dendritic and T helper 17 (Th17) cells, results in persistent cytokine release, particularly IL-17 and IL-23, which drive continuous keratinocyte proliferation and abnormal epidermal differentiation. In simple terms, these immune signals tell skin cells to grow and divide much faster than normal. Rather than undergoing normal maturation, keratinocytes accumulate rapidly on the skin surface, forming thickened, well-demarcated plaques covered with adherent silvery scales (Feng & Liao, 2025). These plaques may fissure, bleed, or become intensely pruritic, contributing to discomfort and secondary skin irritation. The disease follows a relapsing-remitting course, meaning symptoms improve for periods of time but then return in episodes known as flares. Flares are commonly triggered by psychological stress, infection, skin trauma, seasonal changes, or medication exposure. During exacerbations,

lesions often enlarge, increase in erythema and thickness, and may spread to previously unaffected areas. The timing and severity of these flares can vary widely among individuals. Flares may last several weeks to a few months, while periods of remission, when symptoms improve or largely disappear, can last months or even years, particularly with effective treatment.

Although symptoms may partially improve with treatment or environmental changes, the underlying inflammatory process remains chronic, making sustained disease control difficult without targeted intervention. Beyond its physical manifestations, psoriasis imposes substantial social and functional limitations. Visible plaques can lead to social avoidance, workplace discrimination, and altered interpersonal interactions. Patients frequently report embarrassment, self-consciousness, and anxiety, particularly when lesions involve the scalp, hands, or face. Functionally, plaques affecting the palms, soles, or joints can impair mobility, manual tasks, sleep quality, and occupational performance. Thus, psoriasis represents not only a dermatologic condition but a chronic inflammatory disorder with significant psychosocial and functional consequences that extend well beyond the skin. Currently, psoriasis is treated with a combination of topical therapies, phototherapy, systemic medications, and targeted biologic agents that inhibit key inflammatory pathways such as TNF- α , IL-17, and IL-23 (Chan, 2025; Armstrong & Read, 2020). By aligning therapeutic action with specific molecular drivers of disease rather than broadly suppressing immune activity, biologic therapies represent a shift toward precision-based intervention in psoriasis management.

Biologic and Systemic Therapies

Historically, psoriasis management has been guided by disease severity. For mild psoriasis, treatment typically begins with topical therapies such as corticosteroids and vitamin D analogues, which help reduce inflammation and slow the excessive growth of keratinocytes. For moderate disease, ultraviolet (UV) phototherapy is often used to reduce skin immune activity and improve plaque thickness and scaling. For moderate-to-severe psoriasis, systemic medications such as methotrexate, cyclosporine, and acitretin may be prescribed to suppress immune-mediated inflammation throughout the body. Many of these earlier systemic therapies were developed before the molecular pathways underlying psoriasis were fully understood and therefore work through broad immunosuppression rather than targeting specific inflammatory pathways (Liang et al., 2026). Although these treatments can reduce inflammation and slow keratinocyte proliferation, their mechanisms are relatively nonspecific and are often limited by cumulative toxicity, variable treatment response, and logistical challenges, particularly in the case of frequent phototherapy sessions.

Comparative clinical trial data illustrate meaningful differences in therapeutic efficacy across treatment classes. Traditional systemic agents such as methotrexate achieve PASI 75 responses in approximately 35.5% of patients (Saurat et al., 2008), while oral phosphodiesterase-4 (PDE4) inhibition with apremilast achieves PASI 75 in 28.8% of patients (Papp et al., 2015). While these oral systemic therapies represented an important step beyond topical and phototherapy-based management, advances in immunology led to the development of more targeted treatments. Beginning in the early 2000s, biologic therapies were introduced to specifically inhibit key inflammatory pathways involved in psoriasis pathogenesis, including tumor necrosis factor (TNF- α) and interleukin signaling pathways. These agents marked a major shift toward

precision-based treatment by directly targeting the immune signals responsible for chronic skin inflammation. More recently, targeted small-molecule therapies have continued to emerge. The newer tyrosine kinase 2 (TYK2) inhibitor, deucravacitinib, blocks a signaling enzyme involved in cytokine pathways such as IL-23 and type I interferons that contribute to psoriasis inflammation. Clinical trials have demonstrated improved outcomes, with deucravacitinib reaching PASI 75 in 58.4% of patients at Week 16 (Armstrong et al., 2022), reflecting advances in precision immunology. Biologic therapies demonstrate substantially higher clearance rates and faster onset of action compared with traditional systemic treatments. IL-17 and IL-23 inhibitors, including secukinumab, guselkumab, and risankizumab, achieve greater than 70% skin clearance within 16 weeks, with secukinumab reaching PASI 90 rates of approximately 79% (Gordon et al., 2018; Langley et al., 2014; Reich et al., 2017). This represents a major shift in therapeutic expectations. Historically, psoriasis treatments were evaluated using the PASI 75 benchmark. The ability of newer biologic therapies to consistently achieve PASI 90 or higher reflects a significant advancement in treatment efficacy, as patients now frequently experience near-complete skin clearance rather than partial improvement.

At the same time, biologic therapies were developed to overcome many limitations associated with earlier systemic treatments. Traditional systemic agents such as methotrexate and cyclosporine are associated with potential adverse effects, including liver toxicity, kidney dysfunction, hypertension, and increased risk of infection, particularly with long-term use. Biologic therapies also carry potential adverse effects, although their targeted mechanisms often result in more predictable safety profiles than older systemic medications. Common side effects include injection-site reactions, upper respiratory infections, headache, and mild gastrointestinal symptoms. Because biologics modulate specific immune pathways, they may also increase susceptibility to certain infections, particularly when immune signaling is suppressed over prolonged periods. However, clinical trials and long-term safety studies demonstrate that IL-17 and IL-23 inhibitors are generally well tolerated with lower risk of liver or kidney damage and require less laboratory monitoring.

Reviews of therapeutic development emphasize that improved understanding of cytokine-driven inflammation enabled the creation of agents with superior efficacy and improved safety profiles compared with older systemic treatments (Feng & Liao, 2025). However, prescribing analyses suggest that despite their clinical superiority, biologic therapies are not uniformly utilized. Factors such as high treatment costs, insurance authorization requirements, limited specialist access, and geographic disparities may restrict patient access to these therapies, potentially limiting their overall impact on disease management and patient outcomes.

Patient Satisfaction and Quality of Life

Improvements in skin severity achieved through biologic therapy are closely linked to measurable gains in quality of life. Treatment response is commonly evaluated using the PASI, serving as a modern benchmark for therapeutic success. Achieving PASI 90, is strongly associated with greater reductions in pruritus, physical discomfort, and visible plaque burden—factors that directly influence patient-reported quality-of-life outcomes. Because psoriasis often affects visible areas of the body and can cause persistent symptoms such as itching and pain, improvements in skin clearance can translate into meaningful psychological and social benefits for

patients (Armstrong & Read, 2020). Quality-of-life outcomes in psoriasis are commonly measured using validated instruments such as the Dermatology Life Quality Index (DLQI) and the Psoriasis Disability Index (PDI). These scales evaluate how psoriasis affects daily functioning, emotional well-being, social relationships, and work productivity. Studies consistently show that higher levels of skin clearance, particularly PASI 90 or greater, are associated with significantly improved DLQI scores and reductions in disease-related emotional distress (Armstrong & Read, 2020; Strober et al., 2019).

Beyond short-term clearance, long-term disease control is critical in a chronic relapsing condition such as psoriasis. Sustained remission reduces flare frequency, minimizes cumulative inflammatory burden, and decreases the visibility of lesions that contribute to stigma, anxiety, and diminished self-esteem. For many patients, consistent disease control translates into improved occupational performance, interpersonal relationships, and overall quality of life (Strober et al., 2019). However, real-world prescribing data indicate that biologic therapies are not uniformly utilized across patient populations (Feng & Liao, 2025). Disparities in access—often influenced by insurance coverage limitations, socioeconomic status, racial and ethnic inequities, and cost-related barriers—may restrict the availability of these therapies despite their demonstrated efficacy (Takeshita et al., 2017; Armstrong et al., 2021). Such disparities suggest that barriers to prescription, rather than therapeutic limitations, may prevent certain populations from achieving optimal disease control and quality-of-life improvement. Addressing these inequities is essential to ensure that the clinical benefits of biologic therapy are fully realized across diverse patient groups.

Limitations

Several limitations should be considered. First, much of the supporting evidence derives from randomized clinical trials, which often include carefully selected patient populations and controlled conditions that may not fully reflect real-world clinical practice. Trial participants may have better treatment adherence than broader patient populations, potentially limiting generalizability. Second, comparative studies frequently focus on short-term endpoints, such as 12- to 16-week clearance rates, which may not adequately capture long-term durability, especially because this is a relapsing-remitting disease. These measures may also fail to reflect differences in cost-effectiveness across diverse demographic groups, as many clinical trials enroll relatively homogeneous populations and underrepresent patients with varying socioeconomic backgrounds, comorbidities, or access to care, limiting the ability to evaluate how these therapies perform across broader real-world populations. Socioeconomic background refers to factors such as income, education level, and employment status, which can influence whether patients can afford medications, maintain insurance coverage, or attend follow-up appointments. Comorbidities may complicate treatment decisions, affect how patients respond to therapy, or increase the risk of side effects. Access to care refers to whether patients are able to obtain specialist visits, biologic medications, and consistent monitoring; limited access may delay treatment initiation, reduce adherence, or lead to discontinuation of therapy. As a result, these factors can directly influence treatment effectiveness and health outcomes outside of controlled clinical trial settings. Additionally, disparities in prescribing patterns of biologic therapies complicate the interpretation of outcomes, as they may reflect multiple barriers to access. Acknowledging these limitations

is important because transparent discussion of methodological and population constraints helps clarify how such factors may affect the interpretation and generalizability of study findings. Finally, while quality-of-life improvements are strongly associated with skin clearance, psychosocial outcomes can be influenced by external factors not fully controlled in clinical research.

Biologic Therapies: Call to Action

The evidence indicates that biologic therapies not only outperform non-biologic treatments in achieving higher levels of skin clearance but also translate these clinical improvements into meaningful, functional, and psychological benefits. By targeting central inflammatory pathways, biologics offer sustained disease control that reduces flare frequency, improves visible plaque burden, and enhances overall quality of life in adults with moderate-to-severe psoriasis (Armstrong et al., 2022). Although biologic therapies demonstrate clear clinical superiority in many measured outcomes, continued research addressing long-term safety, real-world effectiveness, cost barriers, and equitable access is essential to fully optimize psoriasis management.

Future investigations should also prioritize diverse patient populations and longitudinal studies to better understand how these therapies perform across different clinical settings and demographic groups, ultimately guiding more personalized and equitable treatment approaches. In addition, healthcare systems, insurers, and policymakers should work to reduce financial barriers associated with biologic therapies, which remain expensive and may limit access for many patients. Expanding insurance approval pathways and increasing pharmacy distribution networks could improve nationwide access to these medications and allow more patients to benefit from effective treatment. Greater provider and patient education regarding the safety profiles, potential side effects, and long-term benefits of biologic therapies is also essential to support informed decision-making and appropriate prescribing practices. Clinicians should ensure that patients are presented with multiple treatment options and that prescribing decisions are guided by clinical need rather than cost restrictions alone. By improving access, increasing education, and expanding inclusive research efforts, the medical community can help ensure that advances in biologic therapy translate into more equitable and effective psoriasis care.

References

- Armstrong, A. W., Foster, S. A., Comer, B. S., Lin, C. Y., Malatestinic, W. N., & Burge, R. (2021). Real-world health outcomes in psoriasis patients treated with biologic therapies: A systematic review. *Dermatology and Therapy*, 11(2), 629–646. <https://doi.org/10.1007/s13555-021-00496-5>.
- Armstrong, A. W., Gooderham, M., Warren, R. B., Papp, K. A., Strober, B., Stein Gold, L., Lebwohl, M., Thaçi, D., Merola, J. F., & Deodhar, A. (2022). Efficacy and safety of deucravacitinib, an oral TYK2 inhibitor, in moderate-to-severe plaque psoriasis. *New England Journal of Medicine*, 386(2), 131–142. <https://doi.org/10.1056/NEJMoa2103625>.
- Armstrong, A. W., & Read, C. (2020). Pathophysiology, clinical presentation, and treatment of psoriasis: A review. *JAMA*, 323(19), 1945–1960. <https://doi.org/10.1001/jama.2020.4006>.
- Armstrong, A. W., Warren, R. B., & Zhong, Y. (2023). Short-, mid-, and long-term efficacy of deucravacitinib versus biologics and nonbiologics for plaque psoriasis: A network meta-analysis. *Springer Link*. https://link.springer.com/article/10.1007/s13555-023-01034-7?utm_source=chatgpt.comhttps://link.springer.com/article/10.1007/s13555-023-01034-7.
- Chan, J. J. (2025). Psoriasis: an update on topical and systemic therapies. *Australian Prescriber*, 48(3), 87–92. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12187478/>.
- Feng, A. S., & Liao, W. (2025). Differences in rates of prescription for biologic therapy between Hispanic, non-Hispanic White, and non-Hispanic minority psoriasis patients: A cross-sectional study of the Medical Expenditure Panel Survey, 2014–2022. *Journal of the American Academy of Dermatology*. Advance online publication. <https://doi.org/10.1016/j.jaad.2025.10.143>.
- Gordon, K. B., Blauvelt, A., Papp, K. A., Langley, R. G., Luger, T., Ohtsuki, M., Reich, K., Amato, D., Ball, S. G., Braun, D. K., Cameron, G. S., Erickson, J., Konrad, R. J., Muram, T. M., & Nickoloff, B. J. (2018). Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *New England Journal of Medicine*, 375(4), 345–356. <https://doi.org/10.1056/NEJMoa1512711>.
- Kaur, H., Behroozian, T., Lansang, R. P., Caini, S., Doccioli, C., & Abu-Hilal, M. (2025). Biologic and non-biologic therapies for scalp psoriasis: A network meta-analysis of randomized controlled trials. *Dermatology Practical & Conceptual*, 15(2), 4793. <https://doi.org/10.5826/dpc.1502a4793>.
- Langley, R. G., Elewski, B. E., Lebwohl, M., Reich, K., Griffiths, C. E. M., Papp, K., Puig, L., Nakagawa, H., Spelman, L., Sigurgeirsson, B., Rivas, E., Tsai, T. F., Wasel, N., Tying, S., Salko, T., Hampele, I., Notter, M., Karpov, A., Helou, S., & Papavassilis, C. (2014). Secukinumab in plaque psoriasis—Results of two phase 3 trials. *New England Journal of Medicine*, 371(4), 326–338. <https://doi.org/10.1056/NEJMoa1314258>.
- Liang, X., Wang, N., Yang, Q., Shen, X., Qiao, W., Xu, Q., & Luo, Q. (2026). Inhibition of CDC25C attenuates IL-17A-driven keratinocyte hyperproliferation and psoriasis progression. *Biochemical and Biophysical Research Communications*, 802, 153342. <https://doi.org/10.1016/j.bbrc.2026.153342>.
- Novartis. (n.d.). PASI scores. <https://novartis.gcs-web.com/static-files/7d23a5a3-2456-44a4-9dc7-1ac2d125137d>.
- Papp, K., et al. (2015). Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis: Results of phase III clinical trials. *Journal of the American Academy of Dermatology*. https://pubmed.ncbi.nlm.nih.gov/26089047/?utm_source=chatgpt.comhttps://pubmed.ncbi.nlm.nih.gov/26089047/.
- Reich, K., et al. (2017). Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, in moderate-to-severe plaque psoriasis: Results from a phase III trial. *PubMed*. https://pubmed.ncbi.nlm.nih.gov/28057361/?utm_source=chatgpt.comhttps://pubmed.ncbi.nlm.nih.gov/28057361/.
- Saurat, J. H., Stingl, G., Dubertret, L., Papp, K., Langley, R. G., Ortonne, J. P., Unnebrink, K., Kaul, M., & Camez, A. (2008). Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. *British Journal of Dermatology*, 158(3), 558–566. <https://doi.org/10.1111/j.1365-2133.2007.08315.x>.
- Strober, B., Ryan, C., van de Kerkhof, P., van der Walt, J., Kimball, A. B., Barker, J., Blauvelt, A., Valdecantos, W. C., & Langley,

- R. G. (2019). Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. *Journal of the American Academy of Dermatology*, 80(3), 843–850. <https://doi.org/10.1016/j.jaad.2018.09.027>.
- Strober, B., Zhong, Y., Sima, A., Beeghly, A., Eckmann, T., Balagula, E., Zhuo, J., & Lebwohl, M. (2024). Criteria for identifying candidates for systemic psoriasis treatment in the real world: Application of the International Psoriasis Council guidelines in patients in North America. *Journal of Psoriasis and Psoriatic Arthritis*, 10(1), 22–27. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11583168/>.
- Takeshita, J., Wang, S., Shin, D. B., Mehta, N. N., Kimmel, S. E., Margolis, D. J., Troxel, A. B., & Gelfand, J. M. (2017). Effect of psoriasis severity on hypertension control: A population-based study in the United Kingdom. *JAMA Dermatology*, 151(2), 161–169. <https://doi.org/10.1001/jamadermatol.2014.2094>.
- Thaçi, D., et al. (2015). Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe psoriasis in a head-to-head comparison. *Journal of the American Academy of Dermatology*. https://www.sciencedirect.com/science/article/pii/S0190962215016837?utm_source=chatgpt.com <https://www.sciencedirect.com/science/article/pii/S0190962215016837>.
- Van Huizen, A. M. (2022). Methotrexate dosing and outcomes in plaque-type psoriasis: A systematic review. *International Journal of Dermatology*. https://www.tandfonline.com/doi/full/10.1080/09546634.2022.2117539?utm_source=chatgpt.com <https://www.tandfonline.com/doi/full/10.1080/09546634.2022.2117539>.
- West, M. (2025, August 5). PASI score: Definition and how to calculate. *Medical News Today*. https://www.medicalnewstoday.com/articles/pasi-score?utm_source=chatgpt.com <https://www.medicalnewstoday.com/articles/pasi-score>.

Atherosclerotic Risk Factors and Their Impact on Brain Circulation After Cardiac Arrest

Areen Sandhu

Abstract: Sudden cardiac arrest (SCA) is still one of the main causes of death around the world. Whether someone survives depends largely on their health before the event and on what happens during resuscitation. In this paper, the goal is to look at how having diabetes or high blood pressure affects the chances of having SCA, and also how these risk factors change the chances of surviving and recovering after an out-of-hospital cardiac arrest (OHCA). Patients with these comorbidities are more at risk for cardiac arrest and less likely to recover well. In addition to these risk factors, there are also external factors that affect outcomes, such as the quality and duration of CPR, how quickly help arrives, and how quickly return of spontaneous circulation (ROSC) is achieved. Studies show that if CPR takes too long or is not done well, people are less likely to survive and more likely to have poor neurological outcomes. There are also important differences between cardiac arrests that occur outside the hospital and those that occur inside. In-hospital patients tend to have better outcomes due to immediate access to medical

professionals and advanced equipment. This further shows the importance of managing pre-existing conditions like diabetes and hypertension early, as well as strengthening emergency response systems. This paper will also propose strategies to improve patient outcomes despite both patient-related and external limitations.

Keywords: diabetes, hypertension, ROSC, brain circulation, cardiac arrest, neurological outcomes

Introduction

Sudden cardiac arrest is a life-threatening medical emergency where an individual's heart stops beating abruptly, halting circulation, resulting in a lack of blood flow to the brain and other vital organs. It is fatal in almost 90% of cases without intervention (Kim et al., 2022). Over 417,000 people experience sudden cardiac arrest yearly in the United States alone (American Heart Association, 2025). The causes vary from patient to patient, including those who suffer from underlying heart disease. This is an important public health topic because understanding key prevention strategies can help increase survival rates and improve patients' quality of life. There are many causes of cardiac arrest in the population, including underlying chronic illnesses. This paper will discuss the impact that preexisting diabetes and hypertension may have on patients who experience sudden cardiac arrest.

Diabetes is a metabolic disease that causes elevated glucose levels, resulting in a weakened vascular system due to chronic hyperglycemia. Hypertension can be defined as having a systolic blood pressure of over 130 mm Hg or a diastolic blood pressure of over 80 mm Hg. Hypertension causes the arteries to be under continuous stress, which can lead to arterial, cardiac, and neurological damage. Often, the same patients who suffer from diabetes or hypertension are at risk for cardiac arrest because of the preexisting vascular system damage. Diabetes mellitus and hypertension are considered major atherosclerotic risk factors because they directly contribute to vascular damage, and an atherosclerotic risk factor is any condition that promotes endothelial injury, impairs vascular reactivity, and increases arterial stiffness. These all result in a weakened vascular system overall, which makes it more difficult for blood to flow effectively. Major risk factors include diabetes mellitus, hypertension, hyperlipidemia, smoking, obesity, and family history. The stress the system already faces from the comorbidities results in a higher risk of sudden cardiac arrest due to an increased risk of coronary heart disease, a leading cause of sudden cardiac arrest. Chronic hyperglycemia causes proteins to undergo a chemical change, leading to inflammation in small blood vessels over time. This leads to accelerated plaque formation and impaired vasodilation. Hypertension causes stress on arterial walls, arterial stiffening, and a change in vascular structure. This impairs the artery's ability to expand under perfusion pressure and respond to CPR.

When there is a severe case of narrowing in the arteries, since oxygen is carried up to the heart through the flow of red blood cells, there is an impaired level of blood flow, and there will be a lack of oxygen reaching the heart. If the heart does not receive enough oxygen to function correctly, ischemia occurs. Ischemia can disrupt the electrical signals that control the heart's rhythm, which can cause arrhythmias, which, in cases like ventricular fibrillation, can be incredibly dangerous. In ventricular fibrillation, the heart's electrical activity is not consistent, and the ventricles are effectively unable to contract and pump blood. Since the heart is not receiving

blood flow, sudden cardiac arrest can occur.

Chances of survival for a sudden cardiac arrest are dependent on the return of spontaneous circulation (ROSC), which refers to the heartbeat coming back and the circulation of blood resuming after a cardiac arrest. When there is a prolonged time to ROSC, blood flow to the brain and other organs is severely reduced. Without proper circulation, oxygen is not able to reach brain cells, which means they cannot produce energy. Without oxygen, brain cells will begin to stop functioning, leading to neurological damage. If there is a large time window from the time of cardiac arrest to ROSC, there can be permanent brain and heart damage.

Having preexisting diabetes and hypertension will affect the time that it takes for spontaneous and brain circulation to return, and this paper will explore how these comorbidities increase the risk for cardiac arrest and decrease the chances of survival, as well as what can be done to mitigate external forces and improve patient outcomes.

Impact of Preexisting Conditions on Risk of Sudden Cardiac Arrest

Having preexisting conditions like diabetes or hypertension can significantly increase the risk of experiencing sudden cardiac arrest and lower the chances of recovery afterward. This is because these comorbidities result in atherosclerosis, arterial stiffness, and weakened myocardial function. In cardiac arrest, there is a sudden halt in circulation, so patients who already have an overall weakened vascular system due to these preexisting comorbidities may not respond as well to resuscitation. These patients already have structural or electrical changes in the heart that make them more likely to go into sudden cardiac arrest.

Kim et al. (2022) demonstrated that individuals with hypertension or diabetes, even at early stages such as pre-hypertension or impaired fasting glucose, face a significantly increased risk of sudden cardiac arrest. Chronic hypertension can lead to arterial stiffening, which impacts the structure of the myocardium, making the heart more susceptible to arrhythmias. Constant high levels of pressure and strain on the arteries make it so that the heart has to work really hard to pump blood, which can deteriorate the structure of the heart after a period of time. This debilitation can disrupt the electrical signaling and rhythms of the heart, which can increase the likelihood of arrhythmias, which can result in sudden cardiac arrest. Diabetes can result in atherosclerosis and narrowed coronary arteries, which impact how effectively oxygen can be delivered to the heart.

Voruganti et al. (2018) found a statistically significant association between diabetes mellitus and lower survival rates following out-of-hospital cardiac arrest, with a pooled adjusted odds ratio of 0.78 (95% CI, 0.68–0.89). Having chronic high blood sugar damages endothelial cells, which can impair vasodilation and overall circulation. High glucose levels over time damage the structure of blood vessels, which makes it difficult for them to widen and constrict, therefore impairing how they can regulate blood flow. During the process of resuscitation from cardiac arrest, vascular responsiveness helps determine how effectively circulation can be restored and how well a person will recover. If vascular function is already compromised, then the restoration of circulation after ROSC may be less effective, which would lead to lower survival rates.

Jang et al. (2016) found that the combination of diabetes

mellitus and cardiac disease was associated with significantly lower survival rates after out-of-hospital cardiac arrest. Studies have shown that diabetes and hypertension both have negative impacts on the vascular system, it is evident that having both conditions together would likely result in even greater structural damage to the cardiovascular system. Since the vascular system's structure may already be impaired, the heart could be less able to respond to defibrillation. The combined previous vascular damage and the circulatory dysfunction would make the heart more vulnerable to electrical inconsistencies, arrhythmias, and sudden cardiac arrest because the heart could be less able to respond to defibrillation. Having these preexisting conditions could prolong the time it takes to achieve ROSC while also compromising cerebral circulation and, therefore, neurological recovery.

Impact of Patient-Related Factors on Response to and Recovery from Sudden Cardiac Arrest

Patient-related factors such as hypertension, diabetes, and other preexisting comorbidities can have a major influence on both survival and recovery. This is relevant because these conditions can have a major impact on how a person responds to CPR. Even after the return of spontaneous circulation (ROSC) is achieved, patients could still experience poor outcomes, including neurological injury, reduced cardiac function, and lower overall survival rates. The patients who have comorbidities such as diabetes and hypertension are also often the same patients with other preexisting factors that can negatively impact recovery, such as coronary artery disease, chronic heart disease, and obesity. Kim et al. found that a large percentage of those who experience cardiac arrest and are able to be resuscitated actually still experience poor recovery outcomes (2016). This shows that achieving ROSC does not necessarily mean that recovery is guaranteed, and as other sources have shown, factors such as preexisting diabetes or hypertension can result in poorer quality of recovery.

One reason recovery may be worse in these patients is that diabetes and hypertension often exist alongside other cardiovascular comorbidities, such as coronary artery disease, chronic heart disease, or vascular dysfunction. These conditions weaken the cardiovascular system and impair the body's ability to maintain blood circulation during and after cardiac arrest. During sudden cardiac arrest, the brain and heart do not have access to oxygen because blood flow has stopped, and that is how oxygen reaches them. If a patient already has impaired circulation or vascular damage before the arrest, their body might be even less able to tolerate the ischemia, which can decrease the chances of survival and also the quality of recovery for those who do survive.

Vammen et al. (2018) found that type 2 diabetes mellitus had a negative impact on neurological injury post-cardiac arrest. This would show that metabolic dysfunction can increase the brain's susceptibility to ischemic damage during and after the sudden cardiac arrest. The diabetic brain showed greater markers of neuronal injury compared to the non diabetic control group, so the results show that having this condition exacerbates the injury. The results show that patients with preexisting diabetes may face a higher risk of poor neurological recovery following OHCA (2018). This is important because reduced brain circulation during cardiac arrest means brain cells do not get the oxygen they need to use the glucose they need to function efficiently. As a result, patients may experience worse neurological outcomes, including the loss of normal brain function or permanent neurological deficits.

Jang et al. (2016) found that having both diabetes and cardiac disease resulted in a significant decrease in survival rates after out-of-hospital cardiac arrest. This is important because it also shows that preexisting comorbidities can impact whether or not a patient survives after out-of-hospital cardiac arrest. The combination of diabetes with other cardiac diseases could result in even more stress being placed on the cardiovascular system, which can make resuscitation efforts less effective and, therefore, recovery more difficult. In addition to suffering neurological injury, patients may also experience issues after ROSC, such as electrical instability and long-term damage to the heart due to the lack of oxygen. Together, these results show that patient-related factors not only affect whether or not cardiac arrest occurs, but also how likely someone is to achieve full recovery afterward.

External Factors That Influence Cardiac Arrest and Recovery

External factors can have a significant impact on survival and neurological outcomes after an out-of-hospital cardiac arrest. Some factors include resuscitation time, and the quality of resuscitation. Other important factors include how quickly CPR is started and whether cardiac arrest occurs inside or outside of a hospital. These have an impact on whether or not ROSC is achieved, and also on the time it takes to achieve ROSC, which can determine what quality of recovery is possible.

Reynolds et al. (2016) found that longer resuscitation durations are linked to lower survival rates and worse neurological outcomes after out-of-hospital cardiac arrest. Poor-quality resuscitation can prolong time to ROSC, which would further reduce the chances of survival and quality of recovery. The study of over 11,000 out-of-hospital cardiac arrest patients found that even though about 35% of patients achieved ROSC, only about 10.8% survived until the time of hospital discharge, and only about 8% left with good neurological outcomes. In contrast, in-hospital cardiac arrests tend to have more favorable outcomes due to immediate recognition, faster initiation of high-quality CPR, and access to advanced medical interventions.

De Graff et al. (2020) found that the most optimal timing for resuscitation efforts to be successful was a short time, within 20 to 30 minutes. The longer the efforts go on, the lower the chances become of a meaningful recovery. Reynolds et al. (2016) also showed that most patients who achieved favorable neurological outcomes reached ROSC within about 37 minutes of professional resuscitation efforts. After that time, the chances of achieving a meaningful recovery decreased significantly.

The timing of CPR also plays a critical role in survival. In out-of-hospital cardiac arrest, there is often a delay before emergency medical services arrive, which means that the patient may go several minutes without circulation unless someone is there to begin CPR immediately. This delay can significantly increase the risk of brain injury, since brain cells start to be damaged within just minutes of not getting oxygen. In comparison, cardiac arrest that occurs inside a hospital often receives faster intervention from trained medical professionals, which can improve the chances of survival and neurological recovery for the patient.

Limitations

Current research on sudden cardiac arrest has allowed for many positive changes, particularly because of the increasing knowledge of the role of comorbidities and their impact on survival and

neurological recovery, but it still leaves important gaps that require further investigation. Many studies focus almost exclusively on out-of-hospital cardiac arrest, with a limited amount of comparison to in-hospital cardiac arrest, and it is definitely clear that more research is needed to fully understand how different combinations of comorbidities, and especially multiple specific atherosclerotic risk factors, affect survival and neurological recovery.

Conclusion: Call to Action and Recommendations

Sudden cardiac arrest is still one of the most lethal medical emergencies that can happen, and survival is influenced by underlying health conditions and external factors. This paper looked at how preexisting conditions, such as diabetes and hypertension, increase the risk of sudden cardiac arrest and how they can affect survival and recovery. Overall, the evidence shows that these comorbidities play a major role in both the likelihood of having cardiac arrest and also the quality of recovery afterward. Research shows that these comorbidities contribute to preexisting vascular damage, impaired circulation, and an increased risk of arrhythmias, which all result in patients being more vulnerable to suffering a sudden cardiac arrest. Additionally, these conditions can result in worse outcomes, due to them causing reduced effectiveness of resuscitation efforts, which could result in an increased risk of neurological injury even if ROSC is achieved. This highlights the importance of immediate intervention due to the fact that even small delays can significantly negatively impact patient outcomes. Moving forward, reducing fatalities will require improved disease management, more preventative cardiovascular care, and well-structured emergency response systems. This includes earlier screening for hypertension and diabetes, management of patients who are at high risk, and improved coordination between pre-hospital and hospital care teams.

External factors, like the quality of CPR, the duration of resuscitation efforts, and the amount of time it takes to begin CPR, have a major impact on survival. When circulation is not restored quickly, the brain and heart experience a prolonged period without oxygen, which can lead to permanent damage. These findings matter because they show how important it is to take preventive measures and how important it is for quality, rapid intervention to take place. Improving the long-term management of these conditions could reduce the overall risk by improving vascular health and reducing cardiovascular stress. This would include strategies like helping patients monitor blood pressure levels better, get screened for possible cardiovascular diseases more often, and get educated on lifestyle modifications that would help them. It is also important to increase public awareness of CPR and for public health initiatives to improve bystander response through targeted education and training. Similar widespread education on how to do the Heimlich maneuver and stroke recognition campaigns like FAST (Face, Arms, Speech, Time) have given the public the tools they need to act quickly in emergencies. Applying this same educational awareness to cardiac arrest by expanding CPR training and increasing access to automated external defibrillators would give bystanders the power and ability to intervene immediately, even before first responders arrive. Improving bystander response requires prioritizing faster recognition and immediate action, ensuring that more individuals can identify a cardiac arrest and respond without much delay. This means making sure help can reach people faster and that there are more people around who know how to react and what to do in an emergency.

By addressing two major parts of the problem, underlying health

conditions and external factors that influence survival post cardiac arrest, the healthcare system may have the potential to improve survival rates and long-term recovery outcomes for patients. Future research should investigate how specific combinations of comorbidities impact time-to-ROSC and neurological recovery, as well as which forms of intervention are most effective in high-risk populations. In terms of policy, currently, there are efforts to have more automated external defibrillators in public space and to have more CPR training programs, with the goal of trying to help people survive sudden cardiac arrest. These things have helped more bystanders step in and have saved more lives. However, access to these resources remains unequal, and many individuals, especially those in underserved communities, lack the training they would need to respond effectively. Increasing the amount of funding for preventative care programs and creating more standardized emergency response protocols is imperative to reduce mortality rates.

References

- Dayea Beatrice Jang, Sang Do Shin, Young Sun Ro, Kyoung Jun Song, Ki Ok Ahn, Seung Sik Hwang, Young Taek Kim, Sung Ok Hong, & Choi, J. A. (2016). Interaction of the diabetes mellitus and cardiac diseases on survival outcomes in out-of-hospital cardiac arrest. *American Journal of Emergency Medicine*, 34(4), 702–707. <https://doi.org/10.1016/j.ajem.2015.12.076>
- de Graaf, C., Donders, D. N. V., Beesems, S. G., Henriques, J. P. S., & Koster, R. W. (2020). Time to Return of Spontaneous Circulation and Survival: When to Transport in out-of-Hospital Cardiac Arrest? *Prehospital Emergency Care*, 25(2), 1–11. <http://doi.org/10.1080/10903127.2020.1752868>
- Kim, Y. G., Roh, S. Y., Han, K.-D., Jeong, J. H., Choi, Y. Y., Min, K., Shim, J., Choi, J.-I., & Kim, Y.-H. (2022). Hypertension and diabetes including their earlier stage are associated with increased risk of sudden cardiac arrest. *Scientific Reports*, 12(1), 12307. <https://doi.org/10.1038/s41598-022-16543-2>
- Kim, Y.-J., Ahn, S., Sohn, C. H., Seo, D.-W., Lee, Y.-S., Lee, J. H., Oh, B. J., Lim, K. S., & Kim, W. Y. (2016). Long-term neurological outcomes in patients after out-of-hospital cardiac arrest. *Resuscitation*, 101, 1–5. <https://doi.org/10.1016/j.resuscitation.2016.01.004>
- Reynolds, J. C., Grunau, B. E., Rittenberger, J. C., Sawyer, K. N., Kurz, M. C., & Callaway, C. W. (2016). Association Between Duration of Resuscitation and Favorable Outcome After Out-of-Hospital Cardiac Arrest. *Circulation*, 134(25), 2084–2094. <http://doi.org/10.1161/circulationaha.116.023309>
- Vammen, L., Rahbek, S., Secher, N., Povlsen, J. A., Jessen, N., Løfgren, B., & Granfeldt, A. (2018). Type 2 diabetes mellitus worsens neurological injury following cardiac arrest: an animal experimental study. *Intensive Care Medicine Experimental*, 6(1), 23. <https://doi.org/10.1186/s40635-018-0193-2>
- Voruganti, D. C., Chennamadhavuni, A., Garje, R., Shantha, G. P. S., Schweizer, M. L., Girotra, S., & Giudici, M. (2018). Association between diabetes mellitus and poor patient outcomes after out-of-hospital cardiac arrest: A systematic review and meta-analysis. *Scientific Reports*, 8(1). <https://doi.org/10.1038/s41598-018-36288-1>

Apollo to Artemis: How Past Spaceflight Disasters Shape Modern Space Missions

Alex Skillman

Abstract: Inside NASA in the 1960s and 1970s, many factors caused the failures of Apollo 1 and Apollo 13; however NASA used those as learning opportunities to prevent the same failures from reoccurring during the Artemis program and beyond (R. Launius, 1994). This study reviews the pressures of Apollo and prevention of these problems and more in Artemis. To get information about Apollo, scientific papers and space magazines were used. For Artemis, mostly news articles and some papers were used to gather information. Using the flight data from Artemis I along with information about the problems that led to the fire of Apollo 1 and the explosion of Apollo 13, there is a change in NASA safety culture and their proactive resolve to fix issues with Artemis before they become a problem to ensure astronaut safety (NASA OIG, 2024). These changes were not just through modernized systems but through clearer communication while constructing the rocket (J. Kauffman, 2001). As the Artemis program is ongoing, further analysis could be done after more Artemis launches occur, as there will be more data available for analysis.

Keywords: Apollo Program, Artemis Program, Spaceflight Safety, Moon Missions

Introduction

In the high-stakes environment of spaceflight, success hinges on the lessons learned during past missions and disasters. The Apollo program was significantly shaped by the intense political pressures of the cold war, which often prioritized strict deadlines over all else (R. Launius, 1994). This systematic pressure led to the Apollo 1 cabin fire and the Apollo 13 oxygen tank explosion (J. Ward, 2015).

While on the launch pad, performing a plugs-out simulation flight in 1967, there was a fire inside the Apollo 1 Command Module. (J. Ward, 2015; NASA, 2024) It was caused by an electrical arc that ignited the netting, used to make sure tools of astronauts did not float around too much in the module (NASA, 2024). In 1969, Apollo 11 happened and the US was the first country to put a man on the moon. The main focus going forward was making everyone feel like going to the moon was a regular occurrence; this was an attempt to prove our superiority over the Soviet Union. Later in 1970, the oxygen tanks onboard Apollo 13 exploded while 200,000 miles away from earth (Lunar and Planetary Institute, 2019). The investigation later revealed that ground hardware testing on the oxygen tanks led to a damaged insulation and a small fracture on the tank that ended with the tanks explosion (Hutchinson, 2015). Both of these failures happened due to lack of good safety protocols and design oversights. This stemmed from the political pressure put on the program by John F. Kennedy during his speech in 1962 about going to the moon. The White House put a quick deadline for the Apollo program at the end of the decade or 1970.

More recently, Artemis I, which flew in 2022, was a huge success in testing all systems without humans onboard. A ton of data was collected during Artemis I to help with planning future Artemis launches such as Artemis II which is planned to be a crewed launch. While all 4 mission objectives were completed,

there were also many problems along with it. To avoid more deadly failures from happening, changes are being put in place. The Artemis program is not afraid to scrub launches which is partially due to the lessening governmental oversight over NASA. The flight vehicle has advanced systems to prevent accidents from happening including the launch abort system, an adjusted capsule hatch, better flight computers, and an adjusted spacecraft atmosphere (S. Mandel, 2019).

The failures of Apollo 1 and Apollo 13 were due to design oversights, ignorance of problems, and looming governmental oversight (R. Launius, 1994). To prevent these from happening again, Artemis has improved systems, procedures, and significantly less governmental oversight (G. Whitman, 2023). This work uses published research and space magazines for Apollo; however the changes made for Artemis will mainly use news articles as the program is currently ongoing.

Apollo

Pressures on Apollo

When JFK entered office, he didn't care much about space; however he did care about the politics between the Soviet Union and the United States of America (R. Launius, 1994). He wanted to close the "Missile Gap" (A. Siddiqi, 2000). He used fake attempts at making peace, relating to space, with the Soviets that made them look like they were monopolizing space for military gain (R. Launius, 1994). This pressure led to the cabin fire of Apollo 1 and this speech by Gene Kranz, Director of NASA Mission Control, "We are the cause! We were not ready! We did not do our job. We were rolling the dice, hoping that things would come together by launch day, when in our hearts we knew it would take a miracle. We were pushing the schedule" (M. Emmanuelli, 2020). After the first Apollo failure, the tightness of the schedule was lessened but still not gone (R. Launius, 1994). During Apollo 13 the pressure stemmed from a desire to probe the lunar missions were routine, even though public enthusiasm for the program had begun to wane (J. Kauffman, 2001). The US proved it could go to the moon, now they must prove that it was easy to do. (L. Hutchinson, 2015). While doing this, upgrades were done on each new flight to the moon and on Apollo 13 there were problems during the upgrade process that led to the explosion (L. Hutchinson, 2015).

Ignoring Possible Problems of Apollo

The disasters in Apollo were not just a random occurrence but were from a series of bad decisions. Concerns over Apollo 1 were raised well before the fire occurred. The Apollo 1 Crew raised concerns about the flammable materials but were shot down by Joseph Shea, The Apollo Program Manager, who maintained that it was still safe when managed (J. Ward, 2015). During the ground test, the chamber, which was designed for five psi of 100% pure oxygen, was tested at 16.7 psi of 100% pure oxygen to match the pressure at sea level (E. Cortright, 1970). The higher pressure made the materials, such as nylon and certain metals, which would have been safe at five psi of pure oxygen, were extremely flammable at 16.7 psi. In addition, the hatch in the chamber was designed to be removed in a 90 second window. During the training to open the hatches in this time frame, the goal was never achieved by the astronauts.

This theme continued into Apollo 13. The main issue during Apollo 13 was oxygen tank no. 2. That tank was made for Apollo

10 by Beech Aircraft and was retrofitted as one of the 2 tanks for Apollo 13. At some point before Apollo 10's launch, the tank was taken out for maintenance and was dropped two inches onto the ground (L. Hutchinson, 2015). The tank was inspected and found to have no damage. Following inspection, it was reinstalled and flown on Apollo 10 successfully. While the inspection found no problems, a small internal fracture in one of the seams was later found. During the preflight testing, the tank was not able to be purged. To purge it the tank heater was turned on and left overnight. The heater was designed for 28 volts and was connected to a 65 volt power supply. This led to temperatures upwards of 1000 degrees inside the chamber. This allowed for an unknown amount of damage to occur inside of the tank, including the wires. When in space, the astronauts had to stir the chamber using the heater and fans. When the fans were turned on the damaged wires had a huge risk of sparking and causing an explosion inside of the chamber.

NASA instituted changes to the culture around NASA as a response to Apollo and Space Shuttle failures. A review board after Apollo 1 identified five areas to improve safety: spacecraft atmosphere, combustible materials, electrical components, hatch design, and overall program management (S. Mandel, 2019). Pure oxygen environments have not been used since Apollo 1. The crew chamber was replaced by a new chamber, with over 1000 changes from the old one (R. Launius, 1994). These changes included removing all flammable materials, and redesigning the hatch. Apollo 13 was equally as important, with many changes happening in Apollo 14 because of it too. The changes included: changing the wiring type, using a less flammable insulation, and a third redundant oxygen tank was added to the module. Changes to how hardware anomalies were communicated were also added, allowing for communication with higher ups at NASA about small daily issues like the chamber being dropped.

Artemis

Pressures on Artemis

In 2004, just one year after the Columbia Space Shuttle explosion, planning for Artemis began with the Orion capsule. Chuck Dingell, Orion Spacecraft Lead engineer, said that following the Columbia Explosion, "[Their] action was intense focus on crew safety." While they also had a renewed sense of crew safety, the program is now also being driven by the new space race. The race between China, Russia, and the United States to land and colonize the moon along with harvesting the resources on the moon (RMG, 2021). While the new space race is just starting, NASA also has to change how they build to fit within their budget. In 1970, NASA received around 4.5% of the government's budget, in 2025 that fell to roughly 0.3% (D. Casey, 2025). Now having a significantly lower budget, NASA has to go back to the moon while still supporting their other programs.

Problems with Artemis

During the Artemis I flight, the heat shield chipped away in over 100 places, (Figure 1), the service module bolt got oxidized (Figures 2 and 3), and 24 instances of uncommanded power disruptions occurred. (NASA OIG, 2024).

Damage Separation Bolt Separation Bolt

In addition to these issues, ML-1 was heavily damaged during the launch. The elevator doors were blown off and heavy interior damage occurred (Figure 4). It took 6 weeks to repair one elevator



Figure 1. Artemis I heat-shield damage: heat-shield loss, including missing chunks, post Artemis I. Source: NASA.

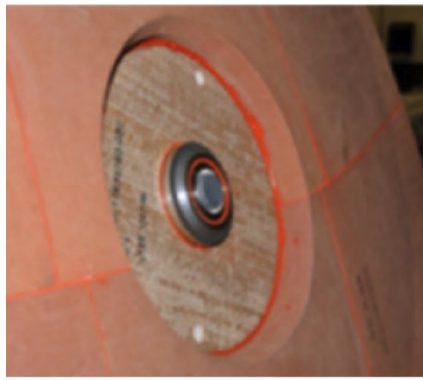


Figure 2. Pre-Artemis I flight separation bolt, before the flight. Source: NASA.



Figure 3. Post-Artemis I flight separation bolt, after the flight. Source: NASA.

and 4 months to repair the other. The elevator doors were fiberglass rather than blast doors; they were designed only to be wind resistant, a factor known prior to the launch (NASA

OIG, 2024).

During the launch the gaseous nitrogen supply was damaged which prevented the blowdown of the internal systems, to purge the noxious gasses, which allowed for days of corrosion to occur inside ML-1 (Figure 5). While in orbit, on day 18, one of NASA's deep space network facilities went down which forced a 4.5 hour loss of communication with the rocket (NASA OIG, 2024). The outage is attributed to maintenance deferrals and deterioration of hardware. In addition to these issues, some of the hardware launched that NASA wished to inspect was not recoverable such as the parachutes and the forward bay cover.

While many problems occurred with Artemis I, Artemis II has been scrubbed several times and at the time of writing launched and is midway through the flight. However the times that have been scrubbed show NASA's willingness to stop a dangerous mission from occurring when they could have an outside incentive or influence to launch it.

Improvements of Artemis

The launch abort system is planned to be attached to the top of the rocket during the Artemis II launch. It was tested during the Pad Abort 1 Test near Las Cruces, New Mexico, where the mock crew capsule was able to fly around a mile away in 135 seconds. To avoid another fire where the astronauts cannot escape, like during Apollo 1, the hatch to enter and exit the crew capsule is lever activated from the inside so astronauts can get out on their own. The flight vehicle also uses a nitrogen oxygen mix similar to the mix at sea level to prevent more unstoppable fires. The separation bolts have heat shielding around them to prevent the rapid oxidation seen on Artemis I from happening on Artemis II. For later Artemis missions, a redesign of the bolt will occur to ensure there is a permanent fix to this issue. The heat shield is more of a mystery that is not yet solved. Engineers are working on a solution to mitigate the chipping seen on the heatshield by changing the geometry or reentry trajectory. (NASA OIG, 2024) Finally, the mission also has the benefit of more advanced flight computers than were ever available to Apollo which are able to better adapt to the current situation the rocket is in.

Conclusion

To prevent failures in space exploration, NASA applied the critical lessons learned from the disasters of the Apollo program to its modern initiatives. The review board following the Apollo 1 fire identified five key areas for safety improvement: spacecraft atmosphere, combustible materials, electrical components, hatch design, and overall program management. As a result, NASA ceased using pure oxygen environments during ground tests, redesigned the hatch to open outward for quick egress, and implemented over 1,000 changes to remove flammable materials from the cabin. The failure of Apollo 13 led to equally significant mechanical changes, including upgraded wiring types, less flammable insulation, and the addition of a third redundant oxygen tank to the service module.

Beyond these mechanical fixes, the tragedies forced a permanent shift in NASA's internal culture to allow for clearer communication and a higher emphasis on safety. Changes to how hardware anomalies are reported now ensure that even small daily issues, such as an oxygen tank being dropped during manufacturing, are communicated directly to high-level leadership. While the Apollo era was often defined by political pressure and a disregard for risk in favor of meeting strict deadlines, the Artemis program utilizes tools like review boards to proactively identify and mitigate risks before they manifest.

Artemis serves as the culmination of these lessons, striving to ensure astronaut safety despite modern challenges such as budget constraints and aging infrastructure. Ultimately, while spaceflight remains inherently risky, the mindset established in the wake of the Apollo failures allows NASA to navigate these risks more effectively than ever before.

References

- Apollo 13 Review Board. (1970, June 15). Report of Apollo 13 Review Board [Review of Report of Apollo 13 Review Board]. <https://web.archive.org/web/20230415005711/https://history.nasa.gov/Ar13cortright.pdf>.
- Dreier, C. (2025). Your Guide to NASA's Budget. The Planetary Society; The Planetary Society. <https://www.planetary.org/space-policy/nasa-budget>
- Howell, E. (2022). 55 years after Apollo 1 fire, NASA's lessons live on as Orion aims for the moon. Space.com.
- Hutchinson, L. (2015, April 16). 45 years after Apollo 13: Ars looks



Figure 4. ML-1 elevator damage: elevator doors on ML-1 after the Artemis I launch. Source: NASA.

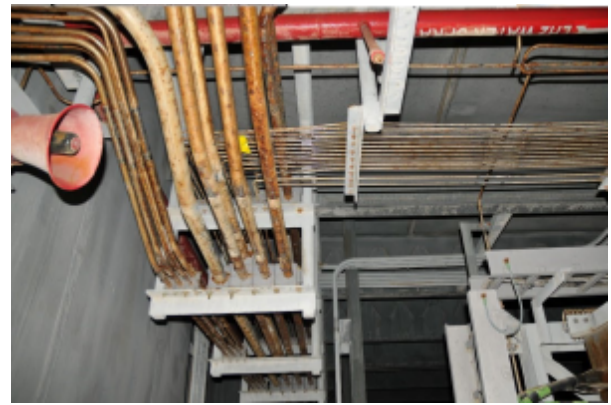


Figure 5. Corrosion inside ML-1: corroded piping inside ML-1 after the Artemis I launch. Source: NASA.

at what went wrong and why. *Ars Technica*; *Ars Technica*. <https://arstechnica.com/science/2015/04/apollo-13-the-mistakes-the-explosion-and-six-hours-of-life-saving-decisions/>

Kauffman, J. (2001). A successful failure: NASA's crisis communications regarding Apollo 13. Launius, R. (2994). *Apollo: A Retrospective Analysis* [Review of *Apollo: A Retrospective Analysis*].

Lunar and Planetary Institute. (2019). *Apollo 13 Mission*. https://www.lpi.usra.edu/lunar/missions/apollo/apollo_13/ Mandel, S. (n.d.). *Trial by Fire: The Legacy of Apollo 1* | American Institute of Physics. [www.aip.org](https://www.aip.org/news/trial-fire-legacy-apollo-1). <https://www.aip.org/news/trial-fire-legacy-apollo-1>

NASA. (2023, November 3). *Apollo 1 - NASA*. NASA. <https://www.nasa.gov/mission/apollo-1/>

NASA OIG. *NASA's Readiness for the Artemis II Crewed Mission to Lunar Orbit*. (2024). <https://oig.nasa.gov/wp-content/uploads/2024/05/ig-24-011.pdf> Siddiqi, A. (2000, September). *Challenge to Apollo: The Soviet Union and the Space Race* [Review of *Challenge to Apollo: The Soviet Union and the Space Race*]. NASA.

The Apollo 1 Fire -. (n.d.). [www.spacesafetymagazine.com](https://www.spacesafetymagazine.com/space-disasters/apollo-1-fire/). <https://www.spacesafetymagazine.com/space-disasters/apollo-1-fire/>

The new space race: a high-stakes competition of politics and power. (2021). *Rmg.co.uk*. <https://www.rmg.co.uk/stories/space-astronomy/new-space-race-astropolitics-power-21st-century>

Ward, J. H. (2015). *Rocket Ranch: Preparations for the First Manned Apollo Mission*.

Whitman, G. A., & Starn, R. P. (2023). Adaptive IV&V reduces risk of software impacting safety in Artemis missions

Understanding Cancer: Synopsis of the Incurable

Euni Kim

Abstract: Globally, cancer is the second leading cause of death with over 40% of people expected to be diagnosed with it in

their lifetime. Due to its complexity, no one has figured out how to cure or prevent it, so millions of people are impacted by this “incurable disease.” Since cancer is a disease that works in many different ways, it is hard to learn and understand all parts of it, but many researchers attempt to make advances in the treatment and understanding of this disease. Our question is how does the understanding of cancer and its characteristics influence the advancement of treatments and tackle the lack of curative measures. Through a search of current literature surrounding cancer, this review will cover the types of cancer, the treatment options, the microbiome's relation, and why there's still no prevention. As cancer is a series of illnesses that has been studied for centuries, the further understanding of cancer will really benefit the advancement of treatments and prevention.

Introduction

In 2026, it is estimated that ~2 million people will be diagnosed with cancer and over 600,000 will die due to cancer. Cancer is not a single disease but a series of diseases, so the understanding of cancer itself is a complex idea to grasp (Upadhaya, 2026). Cancer, being multiple diseases, is organized into 5 categories: **Leukemia** (blood cancer), **Carcinoma** (Lung/breast cancer), **Melanoma** (skin cancer), **Lymphoma** (immune system/blood cancer), and **Sarcoma** (bone cancer). Within these 5 categories, leukemia and lymphomas are noted as non-solid tumors while carcinoma, melanoma, and sarcoma are solid in nature. Depending on the type of cancer a person has, their treatments may also vary. However, although there are treatments for cancer, there is no actual cure. That is because cancer has developed multiple ways to resist treatment. In addition to that, there also is no definite way to prevent cancer.

The difficulties in cancer treatment are highlighted by a group of qualities deemed the “hallmarks of cancer”. The six “main hallmark” abilities of cancer cells are: Sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cancer death. These hallmarks represent the unique ability of cancer cells to progress despite the body's attempt to eliminate them. Additionally, there have been emerging hallmarks recognized which emphasize the growing understanding and complexity of cancer (Hanahan & Weinberg, 2011).

Although there is no definite way to prevent cancer, a strong and diverse microbiome directly impacts carcinogenesis, the multistage

process of normal cells becoming cancer cells, through inflammation, genotoxicity, and immune modulation. The microbiota is also capable of stopping or inhibiting the progression of cancer for it controls the immune responses and other functions. The microbiota is like a “complex and dynamic ecosystem” and is a diverse range of microorganisms. Additionally, the tumor microenvironment (TME), tumor growth, and metastasis has been heavily impacted by the diverse microbiota. In addition, the microbiota interacts with many elements of the TME which impacts the tumor progression (Yanzi Yao et al. 2026).

Since the 1800s, treatment options for cancer have continually advanced. Treating cancer has been and still is a main goal of researchers for many years. Although there isn't a definite treatment, there are a variety of options such as surgery, chemotherapy, and radiation therapy to name a few. Surgery is used for cancers that are solid tumors which for example is carcinoma. Chemotherapy works for both solid and non-solid tumors, they can shrink solid tumors and eliminate other excess cancer cells after another treatment (UT MD Anderson, 2026). Radiation therapy is where they use intense energy to kill or destroy cancer cells (Mayo Clinic). There are more modern methods such as precision medicine therapies, immunotherapy, and targeted therapy. Precision medicine is an approach that uses a patient's individual differences to provide prevention and therapy routes. Both immunotherapy and targeted therapy fall into this category. Immunotherapy is a type of treatment that helps your immune system fight against cancer. Immunotherapy is a biological therapy which is a substance made from living organisms to treat cancer. On the other hand, targeted therapy is a treatment that targets proteins that control cancer cells growth and reproduction. Targeted therapy is the foundation of precision medicine (NCI 2022).

As has been briefly introduced, there are many complex parts in the explanation of cancer. This paper will help achieve a deeper understanding of each specific idea or detail of cancer including what it is, what it does, the types, contributing factors, and treatment options.

Five Categories of Cancer

Throughout the many years of cancer research, many specific types have been discovered and placed into 5 main categories. These categories help researchers better understand disease interaction, treatments, and potential development. The 5 main categories include lymphomas, leukemias, myelomas, carcinomas, and melanomas. Each has its own set of unique properties to be understood.

Lymphoma

First, to start off with, Lymphoma is a group of malignant neoplasms of lymphocytes, vital white blood cells that drive the immune system by fighting abnormal cells. It typically presents itself as a painless adenopathy, with systemic symptoms of fever, unexplained weight loss, and other contributing symptoms. There are about 90 sub-types of Lymphoma, and the two main parts are Hodgkin or non-hodgkin. They were named after Thomas Hodgkin, who first described these abnormalities. Hodgkin lymphoma is almost exclusively a B cell malignancy, and it has four subtypes. On the other hand, non-hodgkin lymphoma is a mix of B and T cells, and it is a much broader sub-type of approximately 140 different types of lymphoma. A lymph node biopsy is the preferred method of diagnosis. Chemotherapy has been the main treatment route for many years. While chemotherapy kills cancer

cells, it damages beneficial ones, which brings many side effects leading to a needed replacement. It has begun to be replaced by immunotherapy because it causes less damage, so there are fewer side effects. A visual explanation would be seen as breaking a door down compared to using a key (William D. Lewis et al., 2020).

Leukemia

On the other hand, Leukemia cancer is when the DNA of a cell mutates or changes in your bone marrow, and there are mass productions of abnormal white blood cells (most are immature cells). Most of the body's blood is created in the bone marrow, and blood cells go through a long process before becoming mature cells. However, in the process if one of the developing blood cells begins to multiply uncontrollably, it becomes Leukemia cells. This abnormality fills the bone marrow and crowds other cells that are trying to mature. When leukemia does happen, it is harder to diagnose or locate for it doesn't show up in imaging tests such as x-rays or CT scans. So, some ways to diagnose leukemia is by taking blood cell examinations, bone marrow biopsy, and physical exams to check for swollen lymph nodes. There are two types of Leukemia: Acute and Chronic Leukemia. Acute Leukemia is when the abnormal cells multiply rapidly and disease progresses quickly. It also is life threatening, and mostly common in children. Chronic Leukemia is when the leukemia cells behave immature and mature, the conditions get worse more slowly compared to acute leukemia and people do not notice symptoms until years later. There are also two main categories for Leukemia based on cell types which include: Myelogenous and Lymphocytic. Myelogenous or myeloid leukemia is when the disease develops from myeloid cells and Lymphocytic leukemia develops from lymphoid cells (Cleveland Clinic, 2022).

Myeloma

Similar to Leukemia, Myeloma is a rare blood cancer that affects your plasma cells (specialize white cells) and create abnormal proteins (or M proteins). Just like Leukemia, Myeloma starts in the bone marrow, however it affects your bones, kidneys, and blood cells. Specialists can treat the symptoms and related conditions, which these treatments slow the cancer's progress. The symptoms can be fatigue and weakness, getting sick easily, numbness or tingling in arms or legs, unexplained weight loss, and nausea and vomiting to name a few. Having Myeloma can cause other medical issues of amyloidosis (proteins damaging organs), cryoglobulinemia (proteins damaging blood vessels), bacterial infections (specifically pneumonia), broken bones, and peripheral neuropathy (nerve damage) to name a few. There are some medical conditions that could require emergency care: hyperviscosity syndrome (when blood is too thick), myelopathy (when bones in your spine are pressing against your spinal cord), and kidney failure. Now, doctors diagnose Myeloma by doing blood tests, urine tests, imaging tests (X-rays and CT scans could show bone damage), a biopsy, or genetic testing. As technology advances there are many treatment options for Myeloma which includes: Stem cell transplant, Chemotherapy, Targeted therapy, Immunotherapy, Steroids, and Radiation therapy (Cleveland Clinic, 2025).

Carcinoma

On the other hand, Carcinoma (the most common type of cancer, 80-90% of people diagnosed) is a solid tumor cancer in which it forms in epithelial tissue (tissue that lines your organs). Carcinoma appears in tumors on your skin, your lungs, breasts, colon, kidneys, or pancreas to name a few. Carcinoma forms solid masses (tumors)

and they spread away from the tumors and spread to other parts of the body. There are 3 labels for describing how much it has spread, which includes: Carcinoma in situ (hasn't spread), invasive carcinoma (spread to surrounding tissues close to where it formed), and metastatic carcinoma (spread to other parts of the body). There are multiple cancers known as "carcinoma," the most common types include: Adenocarcinoma (starts in your glands that line your organs), Basal cell carcinoma or BCC (starts in the basal cell layer of your epidermis), Squamous cell carcinoma or SCC (starts in your epidermis's squamous cell layer), Ductal carcinoma in situ or DCIS (starts in your breast milk ducts), and Invasive ductal carcinoma (starts in your breast milk ducts like DCIS but has to spread to nearby tissues). The risk factors of carcinomas include: exposure to harmful toxins, genetic mutations, and drinking alcohol to name a few. Carcinoma starts with a genetic mutation which goes through carcinogenesis. The cancer cell keeps multiplying and makes more cancer cells which if it is left untreated, the abnormal cells will invade nearby healthy tissues. Then, to diagnose carcinoma, specialists can perform: physical exams, blood tests, imaging (mammogram or colonoscopy), or a biopsy (Cleveland Clinic, 2022).

Melanoma

Although it's not Carcinoma, Melanoma is the most invasive skin cancer with the highest risk of death. Although it is a serious cancer, it is highly curable if it is caught in the early stages. Melanoma means "black tumor" and grows quickly and has the ability to spread to any organ. Melanoma comes from skin cells called melanocytes which these cells produce melanin (dark pigment that gives skin its color). About 30% of this cancer starts in moles, while the rest start in normal skin. Moles can help you predict your skin's risk for developing melanoma. Melanoma only accounts for about 1% of skin cancers but has a great majority of skin cancer-related deaths. It is very common in youth people under 30 (specifically young women). Melanoma could form anywhere on your body, however, men are more prone to developing melanoma on their trunk (often their upper back), and women are more prone to have them on their legs. Melanoma is mostly caused because of overexposure to sunlight. 96% of melanoma are caused by UV rays, and that is because UV exposure can damage the cell's DNA (making changes to genes that support cells to grow). Melanoma can be diagnosed really easily, if you have a mole or a spot that looks suspicious, your doctor or specialist may remove it and look for cancer cells (another words a biopsy) (Cleveland Clinic, 2021).

The differences in these cancer types/categories display one of the main difficulties in understanding and further treating cancer. In addition to these categories, cancer cells have a variety of mechanisms that allow them to progress and bypass the body's immune system. One mechanism is the capabilities and behavior of the microbiome which is crucial to the progression of cancer but also a target for therapy.

Cancer Development and the Microbiome

Through many years of research, the microbiome has played a huge role in understanding the ways cancer is further progressed in the body. The microbiota in cancer represents a complicated ecosystem that has a diverse spectrum of microorganisms (Bacteria, fungi, viruses, etc). The microbiome groups contribute to shaping critical processes such as cancer initiation, progression, metastasis,

and therapeutic responses. It engages both tumor cells and the host immune system, which mediates the local and systemic metabolism and modulates pathways crucial for tumor behavior. The microbiota serves both as potential drivers of carcinogenesis and as targets for therapeutic interventions. The microbiome contributes to the induction of DNA damage and genomic instability. An crucial example of this would be *E. coli* strains having the polyketide synthase genomic island. By creating covalent DNA adducts, colibactin could cause double-strand breaks and interstrand crosslinks. This may increase the mutation burn in host cells and drive colorectal carcinogenesis. There was an experiment done on mice that made them colonize with polyketide synthase-positive *E. coli* have increased tumor formation in the colon, which reinforces the causal role of these bacteria in colorectal cancer progression. Also, the colibactin can also produce ROS and reactive nitrogen species that oxidatively damage DNA bases. On the other hand, the microbiome within tumors may elicit antitumor immune responses by activating immune cells. For example, the presence of specific microbiota might predict better prognoses in PDAC patients. Patients with better prognoses were found to have the characteristics of microbes in their tumors. The microbiota is related to the activation of immune responses and the infiltration of T-cells. Some microbiota enhance or activate certain T-cells in the tumor tissues which strengthens the ability of the immune system to kill the tumor or abnormal cells. The microbiome also plays a role in treatments like surgery, chemotherapy, and radiotherapy. The microbiota can significantly impact the efficacy of chemotherapeutic interventions, and modulate the host immune responses. The intricate interplay between the microbiome and chemotherapy can benefit the integration of microbiota-focused strategies into cancer therapy which improves treatment outcomes. The microbiome can also help or support the effect of radiotherapy with certain bacterial and fungal species either attenuating or enhancing therapeutic outcomes. So, the microbiome's endogenous localization within tumors positions them as supporting candidates for drug delivery vectors, enabling them to navigate the TME, and effectively target cancer cells. The role of the microbiota in cancer is going to become a central theme in cancer research over the next decade (Yao et al. 2026).

Types of Treatments

Cancer is a disease known for its challenging nature to both prevent and diagnose. Roughly 20-30% of cancers are found at the advanced stages (Stage III or IV) which have a statistical increase in mortality rate (Klein et al., 2026). This difficulty in diagnosis is due to there being no effective population-wide screening tests and the presence of symptoms only arising at later development. Additionally, cancer is caused by a variety of factors such as inheritance, lifestyle, exposure to carcinogens which are cancer-causing agents, and most importantly, aging. Overall, due to cancer being a disease based on a person's own cells, prevention and diagnosis is a highly researched area. Despite this, treatment options for cancer are continually being advanced to elevate patient prognosis and quality of life.

Given that there are many types of cancer, there are also many treatment options that are given to people who are diagnosed. Out of the many options, the "golden standards" include surgery, radiation therapy, and chemotherapy. These three treatments are the most known and historical options for cancer treatment. However, recently developed treatments known as precision medicine like immunotherapy and targeted therapy have started to grow as an

option. Here, these treatments will be explained.

Surgery

With solid tumors, the most standard or traditional treatment option is surgery. Doing surgery can mean the surgeon can remove cancers within the body. Surgery is often performed with scalpels and other sharp tools to cut the body during surgery. There are many types of surgeries that can be performed on cancer, however, there are two main types of surgery a person could have. First there could be an open surgery, that is when the surgeon can make a large cut to remove the tumor, although some healthy tissue and nearly lymph nodes (acts as essential fibers) can be removed as well in the process. Then there is minimally invasive surgery in which there are few cuts made and puts a laparoscope (a thin, long tube with a camera) in the small cuts so that the surgeons see what they are doing. As they image and look at what they are doing, they use special tools to take the tumor out and in the process only some healthy tissues are removed alongside it as well. Between the two, minimal invasive surgery would more likely be used for tumors that are in its early stages, and an open surgery would be utilized when the tumors are more serious and dangerous. There are also three main ways surgery works against cancer: the specialist can remove the entire tumor, debulk a tumor, or ease the cancer symptoms. Removing the entire tumor is self explanatory but debulking a tumor means to remove some of the cancer but not all of it for it could damage an organ or the body. Debulking a tumor could help improve the status of the cancer and benefit or help other cancer treatments to kill or destroy the tumor (National Cancer Institute, 2024).

Radiotherapy

On the other hand, there is radiation therapy, another traditional treatment for cancer. Radiation therapy or radiotherapy is a type of treatment that uses beams of intense energy to kill cancer cells. As radiotherapy advanced, the aim of energy was very precise by getting directly to the cancer cells. Radiation therapy can be given in or outside of the body, although the most common kind is external beam radiation therapy. This treatment uses a machine called Linear accelerator, where this machine is able to aim directly to the cancer cells. There is also another type of radiation therapy that goes inside your body called: brachytherapy. This therapy is also common and used by planting a small solid implant in or near the cancer. Although radiation therapy is a commonly used treatment, it damages or destructs cells by destroying the genetic material. Healthy cells could be damaged alongside the cancer cells during the process of radiotherapy. This treatment can treat about every type of cancer, and more than half the people who are diagnosed with cancer will receive or take radiotherapy (Mayo Clinic, 2024).

Chemotherapy

Similar to radiotherapy to certain points, chemotherapy is a type of drug treatment that eliminates cancer cells and controls cell growth. This treatment is best used for cancers that are aggressively and rapidly spreading. Chemotherapy is most commonly used for blood cancers, breast cancers, colorectal cancers, and lung cancers to name a few. This therapy is normally given in cycles, with breaks in between for your body to rest. There are many ways to administer this treatment, one popular method is the Intravenous or IV method (a needle inserted into a vein and attached with a tubing to a plastic bag holding the medicine or drug.) Some IV chemotherapy needs a tube that connects directly to a large vein and is left in place

throughout the treatment. There are many types of ways of delivering chemotherapy, which includes: oral chemotherapy, injections, intrathecal chemotherapy, and isolated limb perfusion to name a few. Although there are many developments and improvements to chemotherapy, there are still many side effects to this treatment. Some of the side effects include: Fatigue, Nausea/vomiting, nerve damage, heart or lung problems, and fertility issues to name a few. So, although it is a well developed treatment, it does have its own issues (UT MD Anderson, 2026).

Precision medicine

Going into more specific and modern treatments, the broad way of coding all the specific treatments is precision medicine which is also known as “personalized medicine.” Precision medicine is a way of preventing or treating a disease based on the person’s genes, environment, and lifestyle. This treatment led to strong new discoveries and improved the chances of survival and reduced exposure to adverse effects (FDA, 2018). This type of treatment was developed by the NIH and their mission is to learn about each individual’s personal genes and lifestyle. This medicine has long and short-term goals. A long term goal includes expanding this type of medicine to all areas of healthcare, and improving healthcare for all people. A short term goal is bringing the medicine to cancer research to study the biology and development of cancer. Since this type of treatment is personalized to you there are many benefits to this treatment which includes: gives a better understanding of why diseases occur, the capability to predict which treatment or therapy may work the best for you, and an improved approach to preventing, diagnosing, and treating diseases. This medicine is used for precision oncology, cancer immunotherapy, pharmacogenomics, and rare diseases to name a few (Cleveland Clinic, 2023).

Immunotherapy

Similar or in the genre of precision medicine, immunotherapy is a type of therapy of treatment that helps your immune system fight off cancer. Immunotherapy is a biological therapy, which uses the substances made from living organisms to treat cancer. This therapy helps and benefits the immune system to detect and destroy cancer cells clearly and effectively. So, as immunotherapy is a modern type of treatment, there are varieties of types of this treatment which examples include: Immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, and immune system modulators to name a few. With these many varieties, there are many side effects, which include: fatigue, itchy skin, diarrhea, and nausea to name a few. Additionally, since there are many types of immunotherapy, there are also multiple ways to administer this treatment. Some ways of giving immunotherapy would be intravenous (IV), oral, topical, and intravesical to name a few. Similar to chemotherapy, immunotherapy is sometimes given in cycles with rest periods depending on the type and stage of cancer you have and how your body reacts to the treatment (National Cancer Institute, 2019).

Targeted Therapy

Another modern treatment is targeted therapy. Targeted therapy is a type of treatment that targets genetic changes or mutations that turn healthy cells into cancer cells. Targeted therapy eliminates abnormal cells without harming healthy cells like chemotherapy or radiotherapy. In this treatment they target specific parts of the cancer cells to treat, which may kill or block the genetic instructions of multiplying. There are many types of Targeted therapy, but the main two are small-molecule drugs or monoclonal antibodies (NIH). There are more than 100 kinds of targeted therapy drugs,

and you may receive them in pills, a shot, or an IV. Now this type of treatment is most commonly used for lung, breast, and prostate cancer, although it can treat other cancers like blood cancers as well. With all these advancements, there are also many side effects of: blood clots, dry skin/rashes, high blood pressure, and loss of hair to name a few. Since there are many many types of targeted therapy drugs, there may be an effective treatment for the cancer one may have (Cleveland Clinic, 2025).

Overall, these treatment options each have limitations marking the inability to cure cancer with a singular approach. In combination, they have been shown to significantly improve outcome and tumor growth inhibition. Despite these advances, translatability to the clinic is seen to be low across multiple different platforms. The vast diversity and complexity of cancer marks its non-curable nature which many researchers are vying to change. Many different aspects of cancer development can be covered, one in which will be discussed below.

Conclusion

In conclusion, cancer is a complex disease in which one could not possibly learn or cover in one sitting. This article covers the five main categories, one particular aspect related to cancer development, and the current state of available treatment. Treatments vary depending on which category they fall under, which add more complexity. There are traditional treatments which have serious limitations despite years of advancement. These limitations have made room for more recent treatments with less defects. Current options are being developed to be personalized for the patient and overcome many hurdles previously seen. Additionally, cell conditions play a crucial role in cancer, such as the microbiome among many more. This review emphasized the advanced nature of cancer and the current practices and work being done to create more understanding and better treatment.

References

- Cleveland Clinic. (2022). Carcinoma: Types, Treatment & What It Is. Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/23180-carcinoma>
- Cleveland Clinic. Leukemia: Symptoms, Types, Causes & Treatments. (2022). Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/4365-leukemia#management-and-treatment>
- Cleveland Clinic. (2021). Melanoma. Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/14391-melanoma>
- Cleveland Clinic. (2022). Multiple Myeloma: Symptoms, What It Is, Prognosis & Treatment. Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/6178-multiple-myeloma>
- Cleveland Clinic. (2022). Sarcoma Tumor: Type, Symptoms, Stages & Treatment. Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/17934-sarcoma>
- Cleveland Clinic. (2022). Targeted Therapy: What It Is, Process & Side Effects. Cleveland Clinic. <https://my.clevelandclinic.org/health/treatments/22733-targeted-therapy>
- Cleveland Clinic. What Is Precision Medicine? (2023). <https://my.clevelandclinic.org/health/articles/precision-medicine>
- FDA. (2019). Precision Medicine. FDA. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine>
- Hanahan, D. and Weinberg, R. (2011). "Hallmarks of Cancer: The next Generation: Cell." Cell, [www.cell.com/fulltext/S0092-8674\(11\)00127-9](http://www.cell.com/fulltext/S0092-8674(11)00127-9).
- <https://grail.com/stories/why-finding-cancers-before-its-too-late-matters-more-than-ever/>
- <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy>
- <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies>
- Klein, E. et al. (2026). Why Finding Cancers Before It's Too Late Matters More Than Ever. Grail.com.
- Lewis, W. D., Lilly, S., & Jones, K. L. (2020). Lymphoma: Diagnosis and Treatment. American Family Physician, 101(1), 34–41. <https://www.aafp.org/pubs/afp/issues/2020/0101/p34.html>
- Mayo Clinic. (2024). Radiation therapy. MayoClinic.org; Mayo Clinic. <https://www.mayoclinic.org/tests-procedures/radiation-therapy/about/pac-20385162>
- MD Anderson Cancer Center. Chemotherapy. (2025). <https://www.mdanderson.org/treatment-options/chemotherapy.html>
- National Cancer Institute. (2019). Immunotherapy to Treat Cancer. National Cancer Institute; Cancer.gov.
- National Cancer Institute. (2015). Surgery. National Cancer Institute; Cancer.gov. <https://www.cancer.gov/about-cancer/treatment/types/surgery>
- National Cancer Institute. (2022). Targeted Therapy to Treat Cancer. National Cancer Institute; Cancer.gov.
- National Cancer Institute. (2021). What Is Cancer? National Cancer Institute; National Institutes of Health. <https://www.cancer.gov/about-cancer/understanding/what-is-cancer>
- Yao, Y., Zhu, Y., Chen, K. et al. (2026). Microbiota in cancer: current understandings and future perspectives. Sig Transduct Target Ther 11, 39 <https://doi.org/10.1038/s41392-025-02335-3>

Little Molecule, Big Impact: How DNA Shapes Modern Medicine

Zelie Little

Abstract: The discovery of DNA in 1868 launched a new era of scientific investigation centered around understanding what DNA is and how it can be used. Through critical contributions such as a groundbreaking picture of DNA taken by Rosalind Franklin known as Photo 51, James Watson and Francis Crick were credited with uncovering the structure of DNA, a breakthrough that won them the Nobel Prize. It has since been understood that DNA is fundamental to life as it is responsible for the genetic makeup of all organisms. From its discovery, extensive research has been done to find DNA's applications in medicine, particularly to develop cancer therapeutics and help cure genetic diseases. By exploring current available literature, this paper gives an overview of what DNA is and shows how DNA fits in with and explains medicine. This can be helpful for readers who want to know more general information about DNA without narrowing in on one specific part of it. Future directions in DNA research include advancing methods

to accurately and effectively modify it, understanding more specific DNA functions, and leveraging knowledge that DNA is altered through generations.

Keywords: DNA, disease, medicine, extraction

Introduction

Nucleic acids are an essential class of macromolecules responsible for storage and expression of genetic information. The most studied types include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) which work together (Bates, 2025). While RNA is needed for protein synthesis and other major cellular roles, there is a higher focus on DNA. DNA is responsible for containing the genetic information of living organisms and interestingly there is only a 0.1% genetic difference that separates one person from another (Schmerker, 2020). It has been understood that DNA determines how an organism develops and functions and any change consequently affects the organism. These changes in DNA can be inherited or caused by outside factors leading to genetic disorders and diseases. Scientists and researchers have explored and are currently exploring DNA and its function to understand many disease states and provide better treatment options.

The Discovery of DNA

Although DNA is central to biology, scientists have not always known what carried genetic information. The discovery of DNA includes multiple events and people. The first identification of DNA came in 1869 when Friedrich Miescher discovered nuclein which was later named DNA in his work regarding white blood cells. In the years to follow, scientists such as Phoebus Levene, Oswald Avery, Erwin Chargaff, and others made integral observations to further build the knowledge on DNA (Pray, 2008). Notably, James Watson and Francis Crick won the Nobel Prize for discovering the structure of DNA in 1953 (Chaikovsky, 2016). This was done through extensive research, and an especially important breakthrough was made by Rosalind Franklin who took a photograph of DNA, which is famously known as Photo 51. This photograph was unique in that it gave a very good depiction of the double helix structure of DNA. It is now known that DNA is composed of two separate strands wound around each other resembling a twisting ladder. These strands are composed of alternating phosphates and sugars with bases attached to each sugar. The bases project out from the strand and form a bond with the bases on the other strand. There are four bases: adenine, cytosine, guanine, and thymine. Together, this described structure revolutionized the understanding and development of molecular biology and modern medicine. This understanding allows scientists to further study genetic diseases and build treatments.

Genetic Diseases

Since DNA codes the genetic information for all living creatures, any accidents when copying DNA can result in genetic mutations. While usually harmless, some of these mutations can have a high negative impact on people in cases termed as genetic diseases. Some mutations are inherited from parents while others can accumulate through one's lifetime. Genetic disorders can be characterized as chromosomal, multifactorial, or monogenic (Cleveland Clinic, 2021). Chromosomal disorders, such as Down's Syndrome and Klinefelter Syndrome, are characterized by missing or duplicated structures responsible for packaging DNA known as chromo-

somes. Multifactorial disorders, such as Alzheimer's, cancer, and diabetes, are characterized by a combination of mutations stemming from chemical exposure, diet, smoking, and other lifestyle factors. Monogenic disorders, such as cystic fibrosis and sickle cell, are characterized by the mutation of a singular gene (Cleveland Clinic, 2021). Studying these diseases and understanding how DNA works provides opportunities for improved patient care.

Current Advances In Nucleic Acid Medicines

There has recently been a rapid development in nucleic acid drugs and therapeutics. In traditional medicine, treatments consist of drugs that influence bodily processes to focus on alleviating symptoms. Nucleic acid medicines, on the other hand, use genetic material to fix the underlying cause of the disease (Zhang et al., 2024). There are several kinds of nucleic acid drugs, including antisense oligonucleotides, small interfering RNAs, microRNAs, aptamers, decoys, and CpG oligodeoxynucleotides (Yamakawa et al., 2019). These can be used to treat various diseases, such as pancreatic cancer. Additionally, various therapeutics such as mRNA vaccines, gene delivery, and genetic engineering strategies like CRISPR work to correct mutations or further edit the DNA to limit harmful effects. These therapies are a few of many methods that highlight the current work and state in nucleic acid therapies. Although research on nucleic acid drugs is far from complete, it continues to be a main focus for potential new treatments.

How Can DNA be Visualized and Used

Although DNA is microscopic and not visible within cells, it is possible to break down the cell membrane and extract the DNA. This can be done with both simple and advanced techniques which give the ability to observe and study DNA. In fact, DNA can be visualized with the naked eye using everyday household items. For example, strawberries are commonly used due to the presence of four times the amount of DNA in their cells compared to human cells. By mashing the fruit and breaking down their cell membrane with a solution of detergent, salt, and water, DNA is released into the solution. By adding cold alcohol, the DNA precipitates into a visible, stringy substance (NHGRI, 2023).

This simple procedure demonstrates one way DNA can be physically extracted and observed, providing insight into structure and properties. Beyond visualization, extraction techniques build the way for more advanced applications such as genetic analysis, disease research, and medical innovations. Understanding how to visualize and use DNA is therefore essential to biological and medicinal advances. This paper aims to give an overall view of how DNA was discovered, what it does, and how it has been and can be used in medicine.

Mechanisms of DNA and How Cancer Affects It

DNA functions as the set of instructions for cells to follow. Stretched end-to-end, the DNA molecules in a single human cell would come to a length of about 2 meters (Anderson and Bartee, 2016). This may not seem like a lot, but a cell is so small that it can't be seen with the naked eye. In other words, there is a lot of DNA for just one cell, and so it needs to be more compact. In order to do this, DNA strands are condensed into a form called chromosomes. There are forty-six chromosomes in one cell and at the end of each chromosome is a long list of base-pairings called a telomere. The telomere does not seem to directly affect any part

of the cell or organism. However, every time the cell splits, the telomere gets shorter and when the telomere is gone, the cell can no longer reproduce and dies. That's where enzymes, specialized protein molecules that accelerate chemical reactions, come into play. In a cancer cell, an enzyme called telomerase is activated. Telomerase repairs the telomere so that the cell can reproduce indefinitely. This enables cancer cells to reproduce quickly and indefinitely, causing them to be very dangerous (Robinson and Schiemann, 2022). This explains one way that cancer affects the DNA and causes trouble.

DNA is often damaged by various genomic factors around it. One of the most common and the most harmful forms is a double-stranded break (DSB). DSBs occur when there is a break in the DNA that tears through both strands of DNA. They are often caused by exposure to harmful chemicals or radiation. If DSBs are left unrepaired they can result in cell death or lead to additional mutations and a higher chance for tumor growth. In normal cells, there is a well coordinated network of signaling cascades known as the DNA damage response pathway which senses damage and transmits signals to activate DNA repair systems. DNA damage is often repaired by either non-homologous end joining (NHEJ) or homologous recombination (HR). NHEJ is an error-prone pathway that is mediated by the direct joining of the two broken ends. HR, on the other hand, gives an error-free pathway that serves as a template for repairing the DNA (Hosoya and Miyagawa, 2014). However, in cancer cells, mutations tend to disrupt these repair pathways. Further disruption leads to the cell losing the ability to properly conduct repair. Eventually, these unrepaired mutations can cause the genes that regulate cell division to not function properly. This allows cancer cells to divide uncontrollably and eventually spread to other tissues (NCI, 2024). Over time, researchers have begun to understand how cancers activate or inactivate crucial DNA damage response proteins. Knowing that many cancers leverage the DNA mechanisms, many approaches are being taken to use these cancer-specific properties for advanced therapy options (Hosoya and Miyagawa, 2014).

Cell Membrane Differences in Normal Cells and Cancer Cells

Another important change occurs in the cell membrane. The cell membrane is a thin, flexible phospholipid bilayer that surrounds the cell and protects the organelles inside it (Datta, 2023). In normal cells, there are a number of proteins inside the cell membrane that allow various substances to enter and exit the cell. However, during tumor development, the phospholipid content of the cell membrane changes. It becomes hardened due to an increase in phospholipids and cholesterol. This changes the fluidity and permeability of the cell membrane which essentially changes the arrangement order of the phospholipid bilayer (Datta, 2023). These changes go unchecked due to the ability of cancer cells to bypass normal cellular processes and allowing them to avoid membrane breakdown. Additionally, this makes it harder for substances to enter the cell which results in drugs being unable to enter and affects the growth and death of the cell. A commonly used method to break down membranes include the use of detergents or detergent-like chemicals. In a therapeutic sense, these are inefficient due to their nature of affecting both healthy and cancer cells. With this information, it is again emphasized that therapies must have specific targeting capabilities.

Use of DNA to Treat Diseases

Normally, when DNA is damaged there are specialized pathways that repair it. These are still present in cancer cells, but they aren't the same. There tend to be defects or abnormalities in the proteins responsible for DNA damage response in cancer cells (Hosoya and Miyagawa, 2014). These changes can be detected in cancer therapies to find and get rid of cancer cells. Many cancer therapies, such as chemotherapy and radiation therapy, rely on the DNA damage that would normally be repaired but isn't because of how the tumor affects normal cell processes. There are multiple cases that show an inactivation of a particular protein or abnormal damage to the DNA indicates the presence of cancer. These kinds of therapies are more reliable than drug therapies that negatively affect both cancer cells and normal cells. As shown in Figure 1, these DNA-based therapies use the defect of DNA repair pathways in cancer cells to their advantage. By inhibiting the remaining repair pathway, cancer cells accumulate more damage until they are no longer able to replicate (Hosoya and Miyagawa, 2014). Since these earlier studies, precision medicine, which is the strategy of selecting therapies that target an individual's genetic mutations, has been implemented to improve this scheme. As understanding grows, more approaches will be developed and increase treatment effectiveness while reducing harm to healthy cells. With this in mind, DNA and its mechanisms will continue to be a main focus in cancer and other disease therapies.

Conclusion

DNA is responsible for the genetic makeup of every living thing. It determines what organisms are, how they develop, and how they are related to one another. This means that any change to the DNA, no matter how small, will have significant consequences, for better or for worse. When the DNA is misinterpreted, it can cause genetic mutations that cause chronic illnesses. On the other hand, if it can be figured out how to change DNA, it might be possible to cure those illnesses. With these hopes, many scientists and researchers have worked to advance therapies to attack DNA-based diseases. Understanding the crucial aspects of DNA mechanisms and cell membrane differences in normal cells compared to cancer cells allows for an enhanced view of how DNA mutations are the ground for these illnesses. This knowledge highlights the advances made and ongoing for therapies and medicines with the use of DNA.

References

- Anderson, C. & Bartee, L. (2016). How DNA Is Arranged in the Cell. Openoregon.pressbooks.pub. <https://openoregon.pressbooks.pub/mhccbiology102/chapter/how-dna-is-arranged-in-the-cell/>
- Bates, S. (2025). Deoxyribonucleic Acid (DNA). Www.genome.gov. <https://www.genome.gov/genetics-glossary/Deoxyribonucleic-Acid-DNA>
- Chaikovsky, A. (2016). X Marks The Spot of the Double Helix. The Dish on Science. <https://thedishonscience.stanford.edu/articles/p1nrlu22e03k7wb34dq6cwbdxsew1x>
- Cleveland Clinic. (2021). Genetic Disorders: What Are They, Types, Symptoms & Causes. Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/21751-genetic-disorders>
- Datta, N. (2023). Breaking Down Tumor Drug Resistance: The Link Between Cell Membrane Changes and Treatment Efficacy.

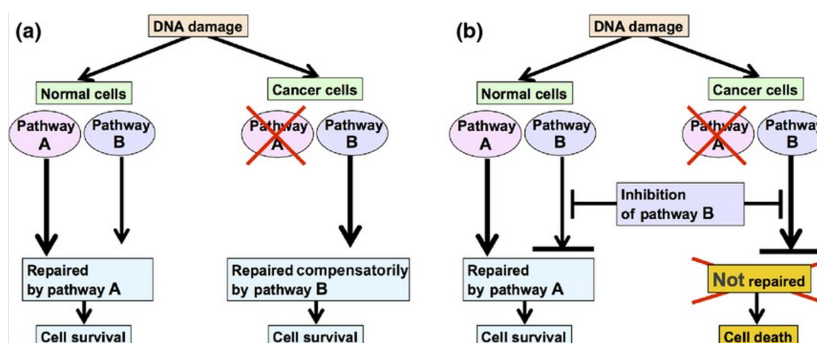


Figure 1. DNA damage is often processed by multiple DNA repair pathways. In the example shown here, pathways A and B are both intact in normal cells, whereas pathway A is defective in cancer cells. (a) In the absence of the pathway B inhibitor, cancer cells can survive, because the defect in pathway A is compensated by the alternative pathway B. (b) When the cells are treated with the pathway B inhibitor, both pathways will be blocked in cancer cells, which will result in cell death. However, normal cells will not be affected, because inhibition of pathway B will be compensated by pathway A.

Figure 1. DNA-based cancer therapies exploit defective DNA-repair pathways so that cancer cells accumulate unrepaired damage until they can no longer replicate (Hosoya & Miyagawa, 2014).

Acta Biologica Marisiensis, 6(1), 21–45. <https://doi.org/10.2478/abmj-2023-0003>

Hosoya, N. & Miyagawa, K. (2014). Targeting DNA damage response in cancer therapy. *Cancer Science*, 105(4), 370–388. <https://doi.org/10.1111/cas.12366>

National Cancer Institute. (2024). The Genetics of Cancer. National Cancer Institute. <https://www.cancer.gov/about-cancer/causes-prevention/genetics>

National Human Genome Research Institute. (2023). Strawberry DNA Extraction. Genome.gov; National Human Genome Research Institute. <https://www.genome.gov/about-genomics/teaching-tools/strawberry-dna-extraction>

Piovesan, A., Pelleri, M. C., Antonaros, F., Strippoli, P., Caracausi, M., & Vitale, L. (2019). On the length, weight and GC content of the human genome. *BMC research notes*, 12(1), 106. <https://doi.org/10.1186/s13104-019-4137-z>

Pray, L. (2008). Discovery of DNA Double Helix: Watson and Crick. *Nature*. <https://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397/>

Robinson, N. J. & Schiemann, W. P. (2022). Telomerase in Cancer: Function, Regulation, and Clinical Translation. *Cancers*, 14(3), 808. <https://doi.org/10.3390/cancers14030808>

Schmerker, J. (2020). 10 Crazy Facts About DNA | IDT. IDT. <https://www.idtdna.com/page/support-and-education/decoded-plus/10-interesting-things-you-probably-did-not-know-about-your-own-dna>

Yamakawa, K., et al. (2019). Development and Clinical Trials of Nucleic Acid Medicines for Pancreatic Cancer Treatment. *International Journal of Molecular Sciences*, 20(17), 4224. <https://doi.org/10.3390/ijms20174224>

Zhang, L., Lou, W., & Wang, J. (2024). Advances in nucleic acid therapeutics: structures, delivery systems, and future perspectives in cancer treatment. *Clinical and Experimental Medicine*, 24(1). <https://doi.org/10.1007/s10238-024-01463-4>

Genetic and Environmental Determinants of ACL Injury in

Female Athletes: Implications for Targeted Prevention and Rehabilitation

Pierson Brant

Abstract: The Anterior Cruciate Ligament (ACL) is a tendon in the knee that stabilizes the joint during movement and resists anterior tibial translation and rotational forces. ACL injuries occur at a higher rate in female athletes than male athletes, with female athletes being eight times more likely to sustain an ACL tear. The consequences of ACL injuries extend beyond the recovery period, possibly leading to long-term outcomes such as early-onset osteoarthritis, decline in athletic performance, loss of scholarship opportunities, and psychological distress, including loss of identity and depression in injured athletes. This literature review examines contemporary research regarding the genetic and environmental factors that influence ACL injury risk in female athletes, as well as assesses how this evidence can guide prevention and rehabilitation strategies. Genetically, polymorphisms in the COL12A1 gene and the ESR1 gene have been associated with altered muscle stiffness and joint laxity. Environmentally, artificial turf surfaces, cold temperatures, and inadequate neuromuscular training elevate injury risk by impairing force production and faulty movement mechanics. Sociocultural barriers, including the reduced access to strength training and prevention measures in female athletics programs, further compound neuromuscular deficits in female athletes that increase injury risk. Evidence-based prevention strategies, including structured neuromuscular warm-up programs, preseason risk stratification, and criterion-based rehabilitation protocols, have been shown to significantly reduce ACL injury incidence. Overall, ACL injuries in female athletes arise from a complicated interaction between genetic predisposition and environmental exposure, with no single factor acting independently. Therefore, effective prevention and rehabilitation strategies must adopt a multifactorial and individualized approach.

Introduction

The anterior cruciate ligament (ACL) is a strong band of connective tissue located in the knee that connects the femur and tibia. It

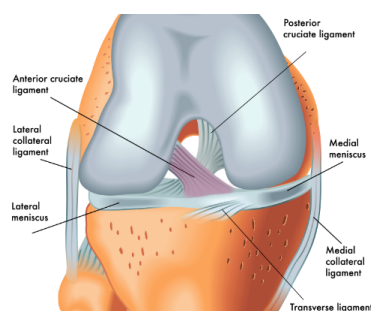


Figure 1. Anatomy of the knee and location of the ACL. From “ACL Anatomy. 2019. Shelbourne Knee Center.”

works to stabilize the knee during rotation or bending by preventing excessive forward movement of the tibia. On a daily basis, the ACL helps maintain stability when walking, turning, or descending steps. In athletic movements, the ACL plays an even more critical role by stabilizing the knee during cutting, pivoting, planting, jumping, rapid changes in direction, and rotating motions.

ACL injuries can occur through either contact or non-contact mechanisms. A contact ACL injury is usually from direct force to the knee. For example, two soccer players colliding knee to knee when trying to get the ball. A non-contact ACL injury can be from sudden deceleration, an awkward landing, or twisting, inward rotation of the knee and the leg when planting. An example of this, from personal experience, is a soccer player jumping up to make contact with the ball and landing on one leg hyperextended underneath her. Three quarters of ACL injuries are non-contact (<https://pmc.ncbi.nlm.nih.gov/articles/PMC3625971/http://et.al, 2010>). These movement patterns increase strain on the ligament and can lead to rupture even without physical contact. The high percentage of non-contact injuries suggests that internal and external risk factors play a major role in ACL susceptibility.

ACL injuries represent a significant and disproportionate problem in female athletics. Female athletes are eight times more likely to suffer an injury to their ACL than male athletes. When a full ACL tear occurs, surgical reconstruction is required to repair the ligament and restore stability to the knee. During this procedure, a surgeon replaces the torn ligament with a tissue graft, typically taken from the hamstring, quadriceps tendon, or patellar tendon. Although surgery repairs the structural damage, it does not immediately restore normal strength or function. After surgical reconstruction, the individual follows a 9-12 month rehabilitation plan to rebuild the strength, neuromuscular control, and joint stability lost in their leg and knee when their ACL was torn. Even with proper rehabilitation, many athletes do not return to their previous level of performance. The long term physical consequences after an ACL tear extend beyond the initial injury and recovery period. Many individuals experience a decrease in the strength, range of motion, and stability of the injured leg and knee. In addition, approximately 50% of patients who have undergone an ACL injury have developed early-onset osteoarthritis (OA) (<https://pmc.ncbi.nlm.nih.gov/articles/PMC7083996/#:~:text=Roughly%20half%20of%20ACL%2Dinjured,reconstruction%20may%20influence%20these%20outcomes>). OA occurs when cartilage that protects the end of a bone wears

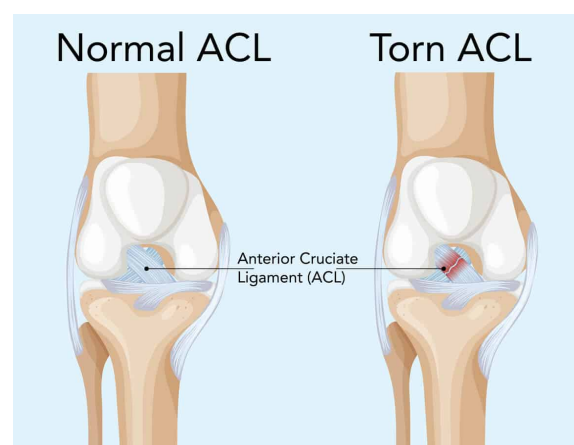


Figure 2. Diagram of a Healthy ACL When Compared to a Torn ACL. From “Signs and Symptoms of ACL Tears in Active Individuals. 2025. UNC Health: Cary Orthopedics.”

down over time (<https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925>). Because cartilage has limited regenerative capacity, joint damage sustained during an ACL injury can accelerate degenerative changes. As OA progresses, pain, stiffness, and inflammation increase, often resulting in chronic discomfort and reduced mobility. OA can be worsened by a number of reasons, joint injury in sports being one of them. Therefore, an ACL tear at a young age can lead to a life of chronic joint pain and functional limitations in the knee.

ACL tears can also result in consequences unrelated to physical ability or pain. The amount of time an ACL injury takes to heal puts athletes out of their sports for up to a year, and taking this amount of time off can lead to a significant loss of conditioning, muscle mass, and sport-specific skills. This can jeopardize scholarship opportunities or other opportunities to further their athletic career because they may never fully regain their skills and athletic function. back. Furthermore, after an injury like this, athletes may never regain their confidence back. For example, only 40% of female athletes, when compared to male athletes, return to sport following an injury. This may be explained by many athletes strongly identifying with their sport, and being unable to participate due to lengthy recovery times can lead to emotional distress. For an athlete, there is nothing worse than not being able to do what you love, so oftentimes, athletes having to take time off to recover from an injury can be extremely hard on their mental health. Nearly half of injured athletes report feelings of loss, frustration, and mild depression after being unable to participate in their sport for at least thirty days (

20of%20reinjury%20are%20also%20common%20responses%20to%20sports%20injuries.&text=In%20fact%2C%20more%20than%203,patients%20reporting%20significantly%20greater%20disturbances.&text=In%20addition%2C%20sports%20injuries%20can,worsening%20preexisting%20body%20image%20concerns.&text=The%20negative%20psychological%20responses%20experienced,to%20intervene%20to%20improve%20outcomes.2023). Therefore, finding a way to reduce the risk of ACL tears is important so that proper prevention strategies can be implemented to protect athletes from the long-term physical and mental distress that come with ACL injuries.

Certain risk factors are known to increase the likelihood of ACL injury in an individual. Intrinsic risk factors include biological and genetic characteristics that influence ligament structure and function, which in turn, modulates the risk of an individual for an ACL tear. For example, collagen gene polymorphisms can alter the structure and organization of collagen fibers, which are responsible for providing strength and flexibility to connective tissues for day-to-day activity and wound healing. Variations in these genes may reduce ligament stiffness or impair tissue repair, increasing susceptibility to tearing. Differences in estrogen receptor gene expression may also influence ligament laxity, inflammation, and tissue remodeling, potentially contributing to the higher rates of ACL injury in female athletes. Additionally, familial predisposition suggests that inherited anatomical or biochemical factors may affect ligament integrity. External factors that increase the likelihood of an ACL tear include factors outside of the control of an individual, such as cold weather, certain artificial turf surfaces, and inadequate warm-up protocols. Certain artificial turf surfaces increase friction between the shoe and playing surface, which can amplify rotational forces at the knee. Cold temperatures may reduce muscle flexibility and increase stiffness, limiting the body's ability to absorb force efficiently. Inadequate warm-up routines or insufficient neuromuscular training can result in poor landing mechanics, knee valgus collapse, and improper muscle activation patterns. When these environmental stressors combine with underlying genetic susceptibility, the likelihood of injury increases significantly. Therefore, ACL injury should not be viewed as a single-cause event, but rather as the result of multiple interacting factors.

This literature review synthesizes evidence on genetic and environmental contributors to ACL injury in female athletes and evaluates how these factors can inform targeted prevention and rehabilitation strategies. By understanding how inherited biological characteristics interact with modifiable environmental conditions, researchers, clinicians, and coaches can design more personalized training and prevention programs, improve neuromuscular conditioning protocols, and implement evidence-based interventions to reduce injury risk.

Genetic Risk Factors Contributing to ACL Injury in Female Athletes

Genetic factors play an important role in determining an athlete's susceptibility to ACL injury because they influence the structure, strength, and mechanical properties of connective tissues and muscles. Collagen is the most abundant protein found in the body, accounting for 30% total protein composition (<https://my.clevelandclinic.org/health/articles/23089-collagen>). Collagen controls the elasticity and strength of connective tissues, such as ligaments, tendons, and cartilage. Because the ACL is composed largely of

collagen fibers, the structure and organization of collagen play a major role in determining the strength and stability of the ligament. The collagen gene (COL12A1) is responsible for producing the alpha-1 chain of type XII collagen, which regulates the arrangement of collagen fibers within connective tissues. When functioning normally, this gene helps maintain the structural integrity and flexibility of ligaments. However, a polymorphism, or variation in the DNA sequence in this gene, could impact joint laxity and muscle strength leading to an increased risk of soft tissue injuries, such as an ACL tear .

Posthumus et al., 2010, investigated whether genetic variation in the COL12A1 gene is associated with an increased risk of anterior cruciate ligament (ACL) rupture, with particular attention to sex-specific effects. The authors conducted a case-control genetic association study including physically active individuals with surgically confirmed ACL ruptures and matched, injury-free controls. These participants were genotyped via PCR for two polymorphisms (AluI and BsrI) in the COL12A1 gene, which encodes type XII collagen, a key structural component involved in ligament organization and strength. The study found that the AA genotype of the COL12A1 AluI polymorphism was significantly overrepresented in female participants with ACL ruptures, increasing their risk for an ACL tear by 2.4 times. There was no such association observed in males or within women for the BsrI variant, suggesting a sex-specific genetic susceptibility. These findings imply that genetic differences affecting collagen structure may explain why female athletes are at higher risk for ACL injuries. This mechanism likely occurs because the COL12A1 organizes primary collagen fibers together and gives a ligament its flexibility and overall strength. The AA genotype of the COL12A1 AluI polymorphism may alter collagen organization, thereby weakening the fibrous bands connecting bones and causing them to lose their elasticity. This can cause hypermobility in joints beyond their normal range of motion. For example, when an athlete plants their foot and pivots, a healthy ACL would stabilize the knee and resist the twisting motion. However, an ACL with a polymorphism in their COL12A1 gene lacks the structural stability and elasticity in their ligament necessary to support their knee, leading to excessive rotation and a torn ACL.

Another gene that plays into the risk of an ACL tear is the Estrogen gene (ESR1). The ESR1 provides the instructions for making estrogen receptor alpha, a specialized protein that acts as a transcription factor when activated by the hormone estrogen. Once bound to estrogen, this receptor travels to the cell's nucleus to directly regulate the expression of specific target genes. This process controls vital cellular functions, like growth, tissue remodeling, and differentiation. It also plays a primary role in the development and maintenance of female reproductive tissues, bone density, and cardiovascular health <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/esr1-gene>. Because estrogen signaling can influence ligament laxity, collagen metabolism, and muscle function, variations in the ESR1 gene may indirectly affect the mechanical stability of the knee joint during athletic movement.

Kumagai et al., 2019 investigated associations between estrogen receptor (ESR1) gene polymorphisms and muscle injury risk and muscle stiffness in athletes. Across two cohorts including over 1300 athletes, the authors analyzed injury history and ultrasound measures of hamstring stiffness in relation to PCR-ESR1 variants. The rs2234693 polymorphism was associated with differences in muscle injury incidence and stiffness, with the C allele demonstrating a protective association. Findings suggest that estrogen-

related genetic variations may influence muscle properties that could indirectly affect injury susceptibility. More specifically, the researchers in this study found that individuals carrying the C allele had a lower baseline hamstring muscle stiffness compared to those with the “TT” genotype. Due to excessive passive muscle stiffness being the primary risk factor for muscle strains and decreased

flexibility, this genetically driven reduction in stiffness inherently lowers the overall likelihood of sustaining a sports-related muscle injury, such as an ACL tear. The study also notes that the C allele is associated with higher ESR1 gene expression, which amplifies the favorable biological actions of estrogen. By enhancing the effects of estrogen, the mechanical properties of connective tissues may be altered, allowing the hamstring muscles to better absorb force and generate more knee joint stability when subjected to physical stress. Consequently, athletes possessing this specific ESR1 variation benefit from a natural protective effect against certain musculoskeletal injuries and ACL tears.

Familial predisposition is another genetic risk factor that can increase susceptibility to ACL tears. Genes are inherited from the parents of an individual, conferring anatomical or physiological traits that make them more susceptible to injury. These inherited characteristics include gendered differences in hamstring strength, increased hip adduction during movement, variations in tibial slope, or neuromuscular control patterns that affect how forces are distributed across the knee joint.

Hasani et al. 2022, investigated if there is a familial predisposition to ACL injuries and if there is a difference in the risk factors in ACL patients with family history to not having family history of injury. The authors performed a systematic review across seven databases to calculate the ratios regarding the association between family history and the risk of primary and subsequent ACL injuries. The study determined that individuals with a family history of ACL injury have a 2.5 times greater risk of sustaining a primary ACL injury, a predisposition that affects both males and females equally. Additionally, these individuals face 2.4 times higher risk of suffering subsequent injuries, including both graft ruptures and tears to the opposite knee. These findings imply that family history of ACL injuries increase an individual’s risk of both ACL tears and re-tears. Therefore, individuals participating in athletic activities should be encouraged to look into their families injury history and participate in prevention programs if a member of their immediate family has sustained an ACL injury in the past.

Genetic traits passed down within families heavily dictate the occurrence of gene polymorphisms, including the COL12A1 and ESR1 polymorphisms. If a family shares a genetic variant in the COL12A1 gene, leading to the disorganization of collagen fibers, the ACL will naturally have an increased susceptibility to injury and require less force to tear. Furthermore, the inheritance of ESR1 may influence joint laxity and passive muscle stiffness. If an athlete inherits hamstrings with high elasticity but insufficient stabilizing strength, the knee may be forced to overcompensate during sudden movements, placing additional stress onto the ACL.

Because athletes cannot change their inherited genetics, targeted prevention programs become imperative to neutralize any increased risk of an ACL tear. Consistent neuromuscular conditioning, including exercises that focus on jump-landing mechanics, balancing, and plyometrics, can improve the body’s unconscious motor response and increase knee stability. Athletes with inherited genetic risk factors should train their stabilizing muscles around the knee to

activate faster and generate more force in order to shield the ACL joint and help compensate for underlying weaknesses caused by inherited genetic vulnerabilities.

Environmental Risk Factors Contributing to ACL Injury in Female Athletes

Outside forces beyond inherited traits also can increase the risk of injury to the ACL. These environmental risk factors influence how forces are applied to the knee joint during athletic movement and can interact with underlying biological susceptibility. One environmental factor that has received increasing attention is infill turf (Turf), an artificial grass material with granular material, most commonly rubber pellets, spread in between the blades of grass. The use of infill turf for sports fields is likely because it guarantees a more consistent playing surface, it can withstand daily use, lowers maintenance, and helps with water conservation. Furthermore, the use of turf for athletics fields has increased significantly in the past several years and the sports turf market is expected to increase at a Compound Annual Growth Rate (CAGR) of 15.4% (<https://www.technavio.com/report/sports-turf-market-analysis#:~:text=The%20sports%20turf%20market%20size,hockey%2C%20rugby%2C%20and%20others.>) As an athlete, playing on a grass field has become rarer and rarer. Many soccer leagues follow a guideline that all matches are to be played on turf fields. While turf does present some benefits, it raises the question of whether these advantages are worth the increased risk of injury for athletes.

Dragoo et al., 2013, investigated the effect of playing on artificial surfaces for NCAA football athletes. In this study the authors gained access to men’s NCAA football ACL injury data and examined it to classify the injuries to see how many occurred when playing on artificial turf surfaces as compared to natural grass. The study found that 87% of ACL injuries occurred on artificial turf surfaces, particularly on surfaces with infill. Additionally, 44% of the documented non-contact ACL injuries occurred on infill turf when compared to natural grass. One explanation for this increased risk is the difference in friction between turf and natural grass. Turf fibers tend to hold onto cleats more firmly than grass, especially when players change direction, rotate, or come to a stop. Because the foot does not release freely from the turf surface, the body’s forward momentum gets redirected to the knee and ankle joints, putting stress on ligaments that can cause them to stretch or tear. Further research should be done to determine whether or not competing on infilled artificial turf directly increases a female athletes’ risk of ACL injuries and if athletes should primarily be competing on artificial or natural grass surfaces.

Seeing as turf may increase the risk of injury in female athletes, changes should be made to make the playing environment safer. One of the most straightforward alternatives to turf is returning to natural grass fields which provides a more forgiving surface that allows cleats to release more naturally during dynamic movements, such as cutting and pivoting, reducing the torque in the joints. For venues where maintaining natural grass is not practical, hybrid turf systems, which weave synthetic fibers into natural grass, attempt to combine the durability of turf with the biomechanical benefits of grass. Continued investment in surface technology, alongside athlete-specific testing, will be essential to determining which alternatives genuinely reduce injury risk.

Knee joint laxity, which refers to the degree of looseness or mobility within the knee joint, reflecting how much the bones,

ligaments and surrounding tissues allow movement beyond normal functional range (<https://www.ncbi.nlm.nih.gov/medgen/39439#:~:text=Definition,from%20NCI%5D.>) One key measure of knee laxity is the anterior tibial translation, which is the forward sliding motion of the tibia (shin bone) relative to the femur (thigh bone) (<https://radiopaedia.org/articles/anterior-tibial-translocation-sign>) This translation occurs without active muscle engagement, and is often produced by an external force. The primary structure responsible for resisting this forward displacement is the ACL, which acts as a mechanical brake to prevent the tibia from shifting too far forward under the femur. When knee laxity is elevated, the ACL must work harder to stabilize the joint, increasing the likelihood of a strain or rupture during athletic movements.

Environmental temperature is another factor that may influence neuromuscular performance and ACL injury risk. Csapo et al., 2017, investigated how cold temperatures affect neuromuscular parameters in muscles and nerves in order to help explain why ACL injuries are more likely to happen in cold conditions. In this study, ten female athlete test subjects underwent a thirty minute period of cooling, before assessing their knee extensor and flexor muscles. Researchers measured these muscles' electromyographic activity, maximum voluntary contraction strength, force sense, passive knee laxity, and rate of force development. The study found that the rate of force development of the knee flexor muscles was reduced significantly after the cooling period.

Explosive force refers to the ability of a muscle to generate maximum force in the shortest amount of time. In sports this is used in actions like sprinting, throwing, and rapidly changing direction. In colder environments, the reduced explosive force capacity of the hamstrings may impair their ability to counteract anterior tibial shear forces during high-impact movements, thus putting strain on the ACL ligament. During movements such as running or landing from a jump, the hamstrings are normally activated just before the foot hits the ground to absorb the impact and stabilize the knee. If the hamstring activation is delayed due to cold temperatures, other structures such as the ACL will be forced to absorb the impact. This creates a delay in the muscles ability to generate the stabilization force and contract fast enough during high impact movements, thus putting additional strain on the ACL ligament. Because temperature has been identified as a clear environmental risk factor, practical strategies to maintain muscle and nerve function in cold conditions should be made a priority in athletic participation. Extended sport-specific warm up protocols are the most accessible intervention for preparing specific muscles used in the sport for performance. Heated sideline gear can also be used to help athletes maintain tissue temperature during stoppages of play. At an organizational level, scheduling games during the winter at an indoor facility rather than having athletes put themselves at risk is a structural solution that removes exposure to cold weather as a variable all together. However, when environmental conditions cannot be controlled the best thing for athletes is to develop their neuromuscular foundation built through targeted strength training. Athletes with stronger muscles, such as the hamstrings, have a larger functional reserve, meaning that even if cold temperatures reduce their explosive output by some margin, their overall stabilization may still be enough to protect the knee joint during dynamic movements. In environments where the temperature cannot be controlled, strength and neuromuscular training can become the athletes primary line of defense.

The hamstring to quad ratio (H:Q) measures the balance of

strength between the hamstring and quadriceps muscles. A healthy H:Q ratio is around 0.5-0.8, meaning the hamstrings should counteract about 50-80% of the force generated by the quadriceps. Values below this range indicate that an individual may have weak hamstring muscles relative to their quad muscles. Having a low H:Q ratio is associated with a high risk of knee injury because the hamstrings protect the ACL by resisting an anterior tibial translation. When the quadriceps contract strongly without sufficient hamstring counterforce, they can pull the tibia forward relative to the femur, increasing strain on the ACL. For this reason, the H:Q ratio is often a key factor for clearing a player for return to sports, after ACL rehabilitation. Ensuring that the hamstring is strong enough to stabilize the knee helps reduce the amount of force transferred directly to the ACL.

Parsons et al. 2021 proposed a gendered environmental framework for understanding ACL injury risk, arguing that sociocultural influences shape many factors traditionally labelled as "intrinsic". The authors demonstrate disparities in training access, strength development, and rehabilitation experiences, and return-to-sport outcomes between male and female athletes. These disparities are shaped by a number of different sociocultural influences, for example, females are encouraged less to participate in strength training and athletics programs. At an institutional level, female athletics programs have historically received less funding, fewer qualified coaching staff, and reduced access to rehabilitation programs. All of these directly affect the quality of injury prevention and recovery care available to female athletes.

Lower participation in resistance training among girls and women, often influenced by gender norms, may contribute to modifiable neuromuscular deficits associated with ACL injury. By integrating gender as a developmental and environmental factor, the paper advocates for greater consideration of how social context influences injury risk and recovery and demonstrates the importance of equitable training and prevention strategies. One of the sociocultural barriers to strength development in female athletes is the stereotype that strength training is masculine, and that muscular physiques are incompatible with femininity. These gender norms are often internalized early in development, discouraging girls from engaging in weight room training during the window in adolescence when neuromuscular habits and movement patterns are being established. Coaching dynamics also contributes to this issue, as female athletes may receive less individualized strength training attention when compared to male athletes in the weightroom. This is especially true in high school teams where oftentimes the strength coach is focused on one team at a time. To shift this trajectory for future generations of female athletes, sports organizations and schools must integrate more strength training programs specifically designed for female athletes, and emphasize that strength development is important not only for aesthetics and performance but also for injury prevention.

Environmental exposures and sociocultural conditions therefore influence neuromuscular strength, movement mechanics, and joint stabilization, all of which can modulate ACL injury risk. These environmental factors often interact with biological predisposition, where athletes who may already have genetic susceptibility to ligament injury could face an even greater risk when exposed to unfavorable training environments, playing surfaces, or social barriers to strength development.

Suggested Prevention and Rehabilitation Measures to Reduce Risk of ACL Injury in Female Athletes

Given the genetic and environmental risk factors that contribute to ACL injuries, it is important to implement prevention and rehabilitation strategies that can reduce injury risk in athletes. One example is neuromuscular training, which includes targeted exercises for improved communication between the brain, nervous system, and muscles. By improving the communication between these systems, coordination, balance, and mobility can be enhanced in athletes. This type of training focuses on proper movement technique, for example, core strength, change of direction, and jump-landing mechanics. ACL injuries commonly occur during rapid changes in direction or errors in movement such as improper landing or knee collapse. Neuromuscular training is an important intervention for athletes because it teaches correct movement form that can be transferred into real game scenarios, such as benefiting bodily reaction to unpredictable movements, thereby reducing the risk of injury. Some examples of exercises that can be used in neuromuscular training to reduce injury risk include box jumps, single leg isolation drills, agility ladders, and jumping-landing exercises. Research from the Hospital for Special Surgery (HSS) has shown that many adolescent athletes are unable to correctly perform common neuromuscular training exercises, with 45% of boys and only 29% of girls demonstrating proper form, highlighting a gender gap in training that may increase injury risk in female athletes (http://www.hss.edu/health-library/move-better/neuromuscular-training#:~:text=Neuromuscular%20training%20programs%20can%20include%20exercises%20that,Concussions%20*%20Ankle%20sprains%20*%20Hamstring%20sprains.) Because ACL tears often are a result of quick changes of direction, landing incorrectly, or cutting and pivoting, implementing neuromuscular training would reduce these movement errors, or non-contact injuries, by training female athletes to execute proper mechanics of movement through repetition.

Gilchrist et al., 2008, in a cluster-randomized controlled trial, investigated whether an alternate warm-up plan for athletes could reduce non-contact ACL tears. In this study, 61 D1 women's soccer teams ($n=1435$ athletes) were randomly assigned to be either a control or intervention group. The intervention groups participated in a neuromuscular warm-up program three times a week. The study found that the ACL injury rate among intervention athletes was reduced by approximately 41% and the non-contact ACL injury rate among intervention athletes was reduced by nearly 70% compared to the control athletes. The intervention athletes faced no ACL injuries during practice, whereas there were 6 cases among the control athletes. During games, non-contact ACL injury rates were reduced by more than half in the intervention athletes. Overall, the study concluded that focusing on neuromuscular control reduces the risk of ACL injuries in high-risk female athletes. Implementing warm-up programs as shown in table one into athletics programs would be highly beneficial and reduce the occurrence of ACL injuries in female athletes. Furthermore, the reduction in ACL tear rates observed in this study shows the importance of advocating for warm up programs structured for neuromuscular training as a standard in female athletics programs. The effectiveness of this intervention is likely due to the targeted emphasis on correcting modifiable risk factors and movement mechanics. Considering these findings, coaches, athletic organizations, and sports medicine professionals have the responsibility of integrating neuromuscular warmup protocols and programs into women's sports.

Pre-season risk stratification is the process of identifying how high or low of a risk a person is for injury, specifically an ACL

injury. This moves intervention from being more “reactive” to “proactive” so that athletes with a higher risk of ACL tears can participate in preventative exercise programs to add an extra layer of protection. Understanding non-modifiable risk factors for ACL injury informs screening strategies for pre-season risk stratification, which include family history, knee laxity assessment, H:Q strength ratios, movement screening, and genetic profiling, allowing intervention to be tailored to each athlete. A family history should be done to see if anyone in an athlete's immediate family has torn their ACL because if they have, an athlete is 2.5 times more likely to tear their ACL. Genetic profiling should be used to identify any inherited genetic variations in collagen or estrogen receptors that would increase an athlete's risk of an ACL tear. A H:Q ratio test, movement screening, and knee joint laxity assessment would identify physical weaknesses that may cause the athlete to have a higher risk of ACL tear. While these variations influence how the body responds structurally and mechanically, early identification through pre-season risk stratification and implementation of tailored prevention strategies focus on strengthening surrounding muscles and improving movement patterns to compensate for these inherited risks.

Medrano et al., 2003, investigated the difference between knee joint laxity and muscular strength between male and female non-athletes. The authors conducted a case control study with fifty four female and male athletes and fifty two female and male non-athletes. These participants underwent anthropometric measurements, dominant-leg determination, and anterior tibial translation assessment using the KT-1000 arthrometer. Participants were asked to kick a soccer ball to determine the dominant leg of each participant. After determining the dominant leg of the participant, the KT-1000 knee arthrometer was used for a knee joint laxity test on the dominant leg. This study found that non-athletes demonstrated greater passive knee laxity than athletes. This suggests that athletic participation may be associated with increased dynamic stabilization or tissue adaptations. Although knee joint laxity is a factor to ACL injury risk, it does not fully explain why female athletes have a higher risk of ACL injuries. The sex differences in peak torque observed in this study suggest that hamstrings capacity relative to the quadriceps demand may also contribute to injury risk. Athletic trainers and coaches should consider addressing these imbalances by targeting hamstring neuromuscular training as a preventative strategy to improve H:Q ratio and strengthen stabilizing muscles. While certain genetic variations and anatomical differences increase the risk of an ACL tear in female athletes are non-modifiable, neuromuscular deficits are, meaning targeted training can raise the threshold at which the knee becomes vulnerable to injury. Integrating screening tools, such as the KT-1000 arthrometer, could help physical therapists or athletic trainers to identify high-risk athletes early and implement targeted conditioning programs.

Early weight bearing (EWB) occurs when a patient who underwent ACL repair surgery begins putting weight on the injured leg within the first few days after surgery. While this might seem like it would further injure the leg, a study by <https://pubmed.ncbi.nlm.nih.gov/38497639/> (2024) determined that EWB does not pose any negative threat to the patient's knee pain, swelling, or wound healing. In practice, EWB improves knee active flexion, the bending of the knee joint, faster and reduces muscle atrophy, especially in the quadriceps and calves. Maintaining muscle strength early in recovery is important because muscle weakness can contribute to poor knee stability following ACL injury.

Return to sport protocol is a phased process after an ACL tear where the patient passes certain criteria in order to begin playing their sport again. The standard program is nine to twelve months of gradual rehabilitation to ensure full healing of the knee and that the athlete is strong enough. An accelerated program however, is six to nine months, with quicker weight bearing and activity. Regardless of the time frame, athletes must reach certain requirements in order to increase their activity level, including 90% muscle symmetry (<https://pmc.ncbi.nlm.nih.gov/articles/PMC8811519/#:~:text=This%20information%20does%20not%20constitute%20medical%20advice,to%20high%2Dlevel%20physical%20activities%20within%206%20months.>) Even though both rehabilitation paths are available to patients, athletes who return earlier or choose to participate in the accelerated program are at a significantly higher risk of re-injury, with some studies suggesting up to a sevenfold increase in ACL re-tear rates. While accelerated rehabilitation allows athletes to return to sport sooner, returning too early before full healing, strength, and neuromuscular control are restored may increase the risk of re-injury.

Adams et al. (2012) reviewed rehabilitation guidelines following anterior cruciate ligament reconstruction (ACLR), emphasizing a criterion-based progression model. This model focuses on achieving specific functional milestones rather than progressing based only on time. He reaffirms the importance of early weight-bearing, progressive strengthening in both weight-bearing and non-weight-bearing contexts, and the use of objective clinical criteria to guide return-to-sport decisions.

Additionally, this paper demonstrates novel feedback regarding meniscal and chondral procedures and underscores the need for rehabilitation specialists and coaches to integrate updated evidence into post-ACLR care and to inform decision-making regarding athletes' ability. A criterion-based progression model is essential to guide rehabilitation decision-making because it is based on the outcomes of the evaluations of the player, assessing not only structural healing, but also strength symmetry, rate of force development, neuromuscular timing, and also psychological preparedness. Strength symmetry between injured and the uninjured leg is critical because asymmetries are strongly associated with reinjury risk, suggesting that a time based criteria is not enough to determine return to sport readiness. Rate of force development and neuromuscular timing are equally important benchmarks, as the ability to generate force explosively and activate stabilizing muscles within a narrow window of dynamic athletic movement reflects the functional capacity of the neuromuscular system in a way that traditional strength testing alone cannot capture. Physiological readiness is an independent predictor of return to sport success, and its exclusion from rehabilitation criteria highlights a gap in standard post-ACL tear care. Female athletes in particular demonstrate a lower return to sport rate following an ACL tear, a disparity that reflects not only potential biological differences in recovery, but also systematic inequalities in access to rehabilitation resources.

Overall, these prevention and rehabilitation strategies demonstrate that while genetic and environmental factors may increase an athlete's susceptibility to ACL injury, many of the key contributors to injury risk are modifiable. Neuromuscular training, pre-season risk stratification, and evidence-based rehabilitation protocols directly target deficits in movement mechanics, strength, and joint stability that were identified in earlier sections. By focusing on both prevention and recovery, these strategies not only reduce the

likelihood of initial ACL injury but also decrease the risk of reinjury and improve long-term outcomes for female athletes.

Discussion

ACL injury risk in female athletes is best understood as a complex multilayered interaction between genetic predisposition, environmental factors, and the effectiveness of prevention and rehabilitation programs. No single factor independently accounts for why female athletes have an elevated ACL injury incidence, rather it is the compounding of multiple risks that add together to elevate an individual athlete's vulnerability. Consider, for example, a female athlete who carries an inherited polymorphism in the COL12A1 gene, has familial history of ACL injury, and regularly trains on artificial turf surfaces in cold weather conditions lacking an adequate warm up protocol. This athlete's cumulative risk profile would be substantially greater than that of an athlete presenting with none or only a subset of these factors. The presence of multiple risks does not render injury inevitable, but it does underscore the clinical value of individualized pre-season screening programs capable of identifying both visible and non-visible risk indicators before competitive season begins. Athletes identified as high-risk through such screening should be prioritized for targeted intervention. While genetic and anatomical risk factors cannot be altered, neuromuscular training and additional individualized exercise programs serve as a critical protective layer to injury by addressing modifiable factors such as movement mechanics, strength, and joint stability.

Given that female athletes have an increased risk of ACL injuries, the implementation of evidence based prevention programs and protocols is necessary at every level of organized competition. Pre-season screening should be established for female athletes competing at higher levels of competition, incorporating genotyping alongside a thorough family history assessment to flag familial predisposition to ACL injury. Biomechanical screening measures, including H:Q ratio assessment and knee joint laxity testing via the KT-1000 arthrometer, should be done in addition to genetic screening to identify modifiable neuromuscular and structural risk factors that may not be clinically apparent through observation alone. Athletes presenting with H:Q imbalances should be enrolled in targeted strengthening protocols designed to address the specific neuromuscular deficiencies identified, while those demonstrating elevated knee joint laxity should be directed toward strengthening programs aimed to improve dynamic joint stabilization. This model of pre-season stratification would allow athletic programs to move towards more individualized prevention strategies that address each athlete's specific risk profile before the competitive season places demand on vulnerabilities.

At a program level, evidence-based warm up protocols, such as those demonstrated to be effective in Gilchrist et al., should be mandatory across all female athletic programs rather than left to the individual coaching staffs. Current warm up programs are often inconsistent, unsupervised, and insufficient in getting the body prepared to compete. Compliance to these programs must be actively monitored, as the protective benefits are contingent on consistency to the warm up protocol. Beyond warm ups, female athletic programs should incorporate mandatory neuromuscular training as a component of athlete development. Additionally, female athletes should be provided with equal access to strength training and development programs, as sociocultural barriers may limit participation in these areas and contribute to neuromuscular

deficits. Strength training programs should emphasize hamstring, hip, and core stability, as these muscle groups play a critical role in protecting the ACL during dynamic movements. At an organizational level, people in power of athletic boards should consider restricting or eliminating competition on artificial turf surfaces, given the evidence linking the high friction of these surfaces to ACL injury incidence. Similarly, athletic organizations should consider ensuring that female athletes, and every athlete in general, are not required to compete in cold weather conditions that may impair neuromuscular performance without access to indoor facilities. The physical impairments associated with cold exposure represent a preventable environmental risk factor that can be addressed.

With respect to post surgical rehabilitation, the accelerated six month return to sport pathway should be discontinued as a path for all athletes post ACL injury. When athletes are presented with a choice between an accelerated and standard timeline for rehabilitation, the psychological drive to return to competition at the earliest opportunity predictably leads most to select the shorter path, even when it carries greater risk of reinjury. Removing this choice and establishing a nine month minimum rehabilitation period as the universal baseline would protect athletes from the consequences of decisions made under competitive drive rather than clinical guidance. Critically, however, the nine month timeline should function as a minimum threshold rather than a fixed discharge, as recovery trajectories may vary between individuals. A criterion based rehabilitation framework should be applied in conjunction with the nine month baseline to ensure that return to sport clearance is determined by the athletes demonstrated achievement of objective functional benchmarks, such as strength symmetry, rate of force development, neuromuscular timing, and psychological readiness, rather than time alone. Athletes who approach the end of the nine month period without meeting established criteria should continue rehabilitation until those benchmarks are completed. This way, long term joint integrity is prioritized and reinjury is prevented.

Several limitations must be acknowledged when interpreting the research reviewed in this paper. Many of the genetic studies examining the environmental and genetic contributors to ACL injury risk have been conducted with a relatively small female sample size, reducing the statistical power needed to draw definitive conclusions about the magnitude and consistency of these associations. Additionally, gene-environment interaction models, which allow researchers to examine how biological predispositions interact dynamically with environmental and training related factors to modulate ACL injury risk, remain largely underexplored in current literature. Despite the accumulation of evidence supporting individualized risk profiling as a promising targeted injury prevention measure, current clinical trials have yet to integrate tools such as genetic screening, biomechanical assessment, and neuromuscular profiling into an athlete specific prevention framework. Until research addresses these gaps through larger and more diverse female samples, gene-environment models, and trials that test individual prevention approaches, the field's ability to translate its findings into equitable and effective injury reduction strategies for female athletes is constrained.

Future research should focus on addressing these gaps. The environmental risk factors are the easiest risk factor to change. The risk turf surfaces should be further researched but with a female sample. Alternative to turf should also be researched in order to find an alternative that still is easy to maintain and cheaper

but does not have such high friction surfaces so that ACL injury risk is lowered. After this research is done, athletics complexes should consider changing the material of their field to better protect their athletes that play there. Furthermore the development and testing of gene-environment interaction models is a critical next step in understanding how genetic predispositions such as collagen gene variations interact with other environmental factors. Research identifying the ideal training hours specific to female athletes is equally necessary, as current guidelines are largely from male athlete data and may not account for the physiological and hormonal factors that influence how female athletes adapt and recover from training stress. The establishment of sex-specific rehabilitation protocols following an ACL tear is another area where further research should be done, given the evidence that female athletes demonstrate lower return-to-sport rates and may face more recovery challenges the generic rehabilitation models are not designed to address. Longitudinal screening programs that track biomechanical, neuromuscular, and genetic risk profiles in female athletes would generate the kind of prospective, population-level data needed to identify when and how injury risk accumulates over time and what stages prevention intervention is most effective. Finally, large scale implementation studies are essential to bridging the gap between what the research recommends and what is actually being practiced in athletic programs at every level of competition.

ACL injury risk in female athletes is driven by the combined influence of genetic predisposition, environmental exposures, and sociocultural factors rather than any single cause. This interaction highlights the importance of individualized prevention strategies, including neuromuscular training, risk screening, equitable access to strength development, and targeted changes to modifiable turf and temperature in the playing environment. Effective rehabilitation must also prioritize criterion-based progression and long-term joint health over rapid return to sport. Ultimately, understanding ACL injury risk in female athletes requires an integrated bio-environmental framework that looks beyond isolated intrinsic or extrinsic explanations and towards individualized, targeted prevention and rehabilitation strategies that target both modifiable and non-modifiable risk factors to reduce injury incidence and improve outcomes for female athletes.

References

- Adams, D., Logerstedt, D. S., Hunter-Giordano, A., Axe, M. J., & Snyder-Mackler, L. (2012). Current concepts for anterior cruciate ligament reconstruction: a criterion-based rehabilitation progression. *The Journal of orthopaedic and sports physical therapy*, 42(7), 601–614. <https://doi.org/10.2519/jospt.2012.3871>
- Boden, B. P., Sheehan, F. T., Torg, J. S., & Hewett, T. E. (2010). Noncontact anterior cruciate ligament injuries: mechanisms and risk factors. *The Journal of the American Academy of Orthopaedic Surgeons*, 18(9), 520–527. <https://doi.org/10.5435/00124635-201009000-00003>
- Cheung, E. C., DiLallo, M., Feeley, B. T., & Lansdown, D. A. (2020). Osteoarthritis and ACL Reconstruction-Myths and Risks. *Current reviews in musculoskeletal medicine*, 13(1), 115–122. <https://doi.org/10.1007/s12178-019-09596-w>
- Cleveland Clinic. (2022). Collagen: What It is, Types, Function & Benefits. Cleveland Clinic. <https://my.clevelandclinic.org/health/articles/23089-collagen>

- Csapo, R., Folie, R., Hosp, S., Hasler, M., & Nachbauer, W. (2017). Why do we suffer more ACL injuries in the cold? A pilot study into potential risk factors. *Physical therapy in sport*, 23, 14–21. <https://doi.org/10.1016/j.ptsp.2016.07.004>
- Dragoo, J. L., Braun, H. J., & Harris, A. H. (2013). The Effect of Playing Surface on the Incidence of ACL Injuries in National Collegiate Athletic Association American Football. *The Knee*, 20(3), 191–195. <https://doi.org/10.1016/j.knee.2012.07.006>
- Du, R., Sun, W., He, F., Jiang, L., Cheng, W., Yu, B., & Chen, J. (2024). Early Weight-bearing Rehabilitation Protocol After Anterior Cruciate Ligament Reconstruction. *Journal of visualized experiments : JoVE*, (205). <https://doi.org/10.3791/65993>
- Gaillard, F. (n.d.). Anterior tibial translocation sign | Radiology Reference Article | Radiopaedia.org. Radiopaedia. <https://radiopaedia.org/articles/anterior-tibial-translocation-sign>
- Gilchrist, J., Mandelbaum, B. R., Melancon, H., Ryan, G. W., Silvers, H. J., Griffin, L. Y., Watanabe, D. S., Dick, R. W., & Dvorak, J. (2008). A randomized controlled trial to prevent noncontact anterior cruciate ligament injury in female collegiate soccer players. *The American journal of sports medicine*, 36(8), 1476–1483. <https://doi.org/10.1177/0363546508318188>
- Hasani, S., Feller, J. A., & Webster, K. E. (2022). Familial Predisposition to Anterior Cruciate Ligament Injury: A Systematic Review with Meta-analysis. *Sports medicine*, 52(11), 2657–2668. <https://doi.org/10.1007/s40279-022-01711-1>
- Joint laxity (Concept Id: C0086437) - MedGen - NCBI. (n.d.). <http://www.ncbi.nlm.nih.gov>. <https://www.ncbi.nlm.nih.gov/medgen/39439>
- Kumagai, H., Miyamoto-Mikami, E., Hirata, K., Kikuchi, N., Kamiya, N., Hoshikawa, S., Zempo, H., Naito, H., Miyamoto, N., & Fuku, N. (2019). ESR1 rs2234693 Polymorphism Is Associated with Muscle Injury and Muscle Stiffness. *Medicine and science in sports and exercise*, 51(1), 19–26. <https://doi.org/10.1249/MSS.0000000000001750>
- Mayo Clinic. (2025, April 8). Osteoarthritis. Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925>
- Medrano, D., Jr, & Smith, D. (2003). A comparison of knee joint laxity among male and female collegiate soccer players and non-athletes. *Sports biomechanics*, 2(2), 203–212. <https://doi.org/10.1080/14763140308522818>
- Parsons, J. L., Coen, S. E., & Bekker, S. (2021). Anterior cruciate ligament injury: towards a gendered environmental approach. *British journal of sports medicine*, 55(17), 984–990. <https://doi.org/10.1136/bjsports-2020-103173>
- Pearle, A. D. (2023, July 19). A Guide to Neuromuscular Training. Hospital for Special Surgery. <https://www.hss.edu/health-library/move-better/neuromuscular-training>
- Posthumus, M., September, A. V., O’Cuinneagain, D., van der Merwe, W., Schwellnus, M. P., & Collins, M. (2010). The association between the COL12A1 gene and anterior cruciate ligament ruptures. *British journal of sports medicine*, 44(16), 1160–1165. <https://doi.org/10.1136/bjsm.2009.060756>
- Sports Turf Market Size, Growth and Forecast. 2023. <http://www.technavio.com>. <https://www.technavio.com/report/sports-turf-market-analysis>
- van Niekerk, M., Matzkin, E., & Christino, M. A. (2023). Psy-

chological Aspects of Return to Sport for the Female Athlete. *Arthroscopy, sports medicine, and rehabilitation*, 5(4), 100738. <https://doi.org/10.1016/j.asmr.2023.04.021>

- Waldron, K., Brown, M., Calderon, A., & Feldman, M. (2022). Anterior Cruciate Ligament Rehabilitation and Return to Sport: How Fast Is Too Fast?. *Arthroscopy, sports medicine, and rehabilitation*, 4(1), e175–

fMRI-Based Deception Detection and Forensic Validity

Ilario Bonelli-Pentangelo

Abstract: Functional magnetic resonance imaging (fMRI) has been proposed as a tool for detecting deception by identifying neural activation patterns rather than skewed observable behaviors. Despite fMRI’s ability to map cognitive activity, deception is a complex social process that often has confounding signals that it shares with other social phenomena, such as arousal; this makes fMRI validity in a forensic setting highly contested. This study aims to identify how fMRI can be enhanced to more reliably detect deception and evaluate a forensic application. Through comparing fMRI deception detection studies, a structured review of task paradigms’ validity, neural regions implicated, and experimental controls was conducted. Importance is placed on studies containing neuropsychological models and those testing applicability to forensic scenarios. Throughout the reviewed research, brain regions associated with executive functioning and truth suppression, like the anterior cingulate cortex and frontal gyrus, consistently inhibited the prediction power of deception. Predictive models that counterbalanced overgeneralization, using dual-goal tuning, fostered moderate success, though results were sensitive to task design and context-dependent variables. Meta-analytical findings on fMRI task-design indicated that tasks with higher ecological validity—tasks which incorporated motivation, social interaction, and intentional deception—reduced confounding signals from other social processes and activated more specific neural networks. Overall, findings suggest the direction of further advancement should be on enhancing fMRI task design and predictive models rather than discovering a single deceptive-specific receptor. Current fMRI approaches remain unsuitable for direct forensic application, but continued methodological improvement could support future investigative practices.

Introduction

Deception is a cognitive process and social-interaction where information is intentionally manipulated (DePaulo, 2003). Traditional research of deception focused on observable behaviours such as facial expressions, fidgeting, physiological responses, etc. This research assumes that individuals exhibit certain observable behaviours when they are in the act of deception; in turn, assuming that it could be observed by a third party. This earlier line of research aimed to identify certain behavioural cues to deception; hesitation, nervousness, pauses in speech, sweating, and fidgeting were some of them. Formulating lies was thought to cause pauses in speech and hesitations, as to come up with or change a story; nervousness and fidgeting were viewed to be signs of an affliction caused by deception. Law enforcement used these behavioural cues

to easily identify deception without special equipment. This can be tied to historical reliance on interrogation and pure intuition, instead of true proof. These assumptions, even used by governments, had little to no empirical evidence, but persisted due to a conflated understanding of this cognitive process and widespread misconception of true deception detection research (Opancina et al., 2024).

Throughout the test of time, there have been many claims of certain methods that truly are able to discover deception. These methods have been found to be outdated and inconsistent; there is an especially large gap between long-standing beliefs about deception (behavioural observation) and what empirical evidence actually shows. Deception in the human body is fundamentally a cognitive process involving executive functioning and inhibitory response. To measure such an activity, internal mechanisms should be used over external signs. This paper examines whether fMRI and other neuroimaging predictors will provide a more valid methodology for detecting deception than traditional means. Using fMRIs is key to finding the specific neural mechanisms activated during deception and their consistency among studies. It is intended to be an evaluation of fMRI, rather than an absolute way to detect deception.

Throughout human history, deception has been a recurring topic of inquiry; however, it remains poorly understood. As it stands right now, modern technology could be leveraged to truly grasp this complexity, allowing deception to be studied on a neural level. Inspecting deception in this capacity will contribute to an understanding of other parts of the brain, like executive functioning. Inaccurate ways of deception detection have led to serious consequences, such as law enforcement using incorrect techniques, leading to wrongful convictions. This paper seeks to test the validity of fMRIs and neuropredictors, a possible stepping stone of deception detection, based on empirical evidence. By examining behavioural and neuroscience findings, this paper aims to identify the true capabilities and limitations of deception detection research.

Literature Characterization

Past Research & Methods of Deception Detection

Cues to Deception (2003), a meta-analysis by DePaulo and colleagues, asks whether people behave differently when they are lying compared to truth-telling. DePaulo and colleagues tested 1,338 estimates of 158 behavioural cues to deception. DePaulo and colleagues also factored in motives like monetary, transgressions, and personal gain. Among these many cues and motives, she found deception to be a very complex and unique process, which made behavioural cues have weak correlations with deception. DePaulo and colleagues found some strong truth-telling correlations between their studies, like cooperative attitudes, genuine smiles, and repetition. The research concluded that the limited number of participants may constrain the real correlations. DePaulo and colleagues rule out behavioural cues of deception and traditional deception detection, narrowing focus towards physiological responses (DePaulo et al., 2003). A major strength of DePaulo et al.'s analysis remains within its scale (1338 cues), allowing for a critical view of long-standing assumptions to be reliable and upheld in high-consequences settings like law enforcement. This study concedes pure human observation, a widely imposed method of identification, as false; this allows the examination of deception to shift to a neural-based procedure.

Throughout the judicial system, many methods of deception detection were used to sentence individuals on trial; one such technique was the polygraph. Polygraphs measure heart rate and skin conductance, synonymous with emotional arousal, not so much deception itself. Polygraphs are not entirely inaccurate as arousal and deception share many confounding signals in the brain, however they may correlate in some areas, but individuals often get false results for being truthful but anxious or trained deceivers. Polygraphs are inadmissible in court as they cannot fully identify deception, thus ruling out polygraphs in continuing deception detection research (National Research Council, 2003).

Plausible Methods of Deception Detection

An article by Opancina and colleagues reviews how advanced neuroimaging techniques might support lie detection in criminal interrogations. The researchers critique previous technology, like polygraphs, as they measure someone's anxiety or arousal rather than deceptiveness. Researchers analyze many methods of neuroimaging—Electroencephalography, fMRI, functional near-infrared spectroscopy, positron emission tomography, and single-photon emission computed tomography. fMRI is highlighted among this group as it measures changes in blood oxygen levels during neural activity with the highest resolution. Researchers cite previous fMRI studies have already pointed out which parts of the brain are used during deception, allowing law enforcement to create differentiated images of truth-telling and deception from brain scans. Opancina and colleagues say this method is limited by confounded signals and other social processes that trigger such parts of the brain (Opancina et al., 2024). This paper directs our approach to fMRIs as they have already been tested in use for detecting deception, as they are also conveyed, by Opancina and colleagues, to have the potential for enhancement.

fMRI as a Use of Deception Detection

Deception is a cognitive process, and as being such, the analysis of deception should involve brain imaging. Brain-based measures can view the foundational brain activity of deception among humans. Distinct from behavioural cues, analyzing deception cognitively could find the commonality of deception in human biology. Neuroprediction shifts research to ask what the brain does during deception, rather than what deception looks like.

Functional magnetic resonance imaging (fMRI) is a method of neuro-prediction, as it detects changes in blood flow and oxygenation—helping to map brain activity. fMRIs identify specific brain regions/receptors activated during certain cognitive processes, activities, and emotions. Deception, a cognitive process, consistently inhibits distinguishable activity from truth-telling in specific brain regions. These regions include the angular gyrus and inferior frontal gyrus. Each of these regions' functions plays a specific role in deception. The angular gyrus (AG), responsible for processing and retrieving knowledge, helps discern truthful and deceptive responses as this section processes the two activities as completely different. The inferior frontal gyrus (IFG) plays a key role in truth suppression. The IFG is important in predictive lying as greater activation means greater truth suppression, which identifies if someone is lying and reveals how skilled they are at deception (Feng et al., 2022). This allows deception to be defined in these regions, narrowing the fMRI analysis of deception in the brain. Feng and colleagues articulate what each of the sections does in relation to deception, which remains important for mapping

different types of deception (distortions, half-truths, untruths), as this may create different activity configurations of these core regions. These implications are critical to the development of the application in forensic and investigative work.

Dual-Goal Tuning is a method/algorithm proposed by Lee and colleagues, which is said to possibly differentiate between deception and other social processes in the brain (Lee et. al., 2024). Dual-goal tuning starts by looking at specific brain regions such as the dorsal anterior cingulate cortex and superior frontal gyrus, which are known to possess predictive power (Lee, 2024). Dual-Goal tuning is proposed as a building block to a forensic application, as it tries to enhance fMRI usage by removing generalizing the area of analysis, whilst trying not to overgeneralize deception and other social processes.

With the understanding that dual-goal tuning seeks to enhance fMRI data, in a pre-print article led by researcher Sangil Lee tests the neuroreceptors related to deception using fMRI and dual-goal tuning. Lee and colleagues create a paradigm that promotes distinction of confounding signals, to not confuse deception with selfishness. This task involves deception trials and non-deception trials, where participants could either lie to another person for benefit, or be forced to engage in non-deceptive, selfish choices for self-benefit. In subject-level prediction—each subject had two discernible images, one of truthfulness and one of deception—they found the methods to be 78.8% accurate. In trial-level prediction—estimated created by algorithms—the predictors still performed above chance at 56.6%. The imperfect results can be attributed to the remaining presence of confounding signals. The researchers add that one formed neural predictor for a certain deceptive situation may be less accurate in another deceptive situation. Lee and colleagues view the results as promising, as certain constructs can be built for certain deceptive behavior (Lee et. al., 2024). Overgeneralization (of confounding signals) is a limitation, as it “lacks discriminant validity,” as the high accuracy does not mean the system is only detecting deception, but instead identifying selfishness in truth-tellers. Overall, the article provides a path to the goal of deception detection, with work still needing to be done, stating that tests with new limitations must be done, with improved dual-goal tuning. Although this version of the study was not peer-reviewed, the analysis remains imperative in understanding the abilities that predictive models like dual-goal tuning should demonstrate.

Another study, also led by researcher Sangil Lee, tests the accuracy of functional MRI-based neural prediction using dual-goal tuning to detect deception. Lee and colleagues use the results from their pre-print study to assess the validity problem of neuroimaging. From this data, they confirm that instead of overgeneralizing, their model actively discriminates deception from a closely matched non-deceptive behavior (Lee et al., 2024). This peer-reviewed article highlights how dual-goal tuning can be used, even in a very harshly paired environment (deceptive v. selfishness greed task), to detect deception. Lee and colleagues propose another method, identifying a specific deceptive receptor, which would be easily distinguishable, but ultimately may not exist. The work in fMRI and dual-goal tuning is promising, but there is still research to be done. Plausible application in the field of forensics is foreseeable in the future, as the quest to detect deception is ongoing, and is necessary for this line of work.

Although dual-goal tuning is a feasible method of deception detection, Delgado-Herrera and colleagues evaluate how task

designs—similar to Lee and colleagues’ work—affect fMRI findings in deception detection. During their analysis of 59 contrasts, researchers found that high ecological validity tasks—tasks that included intention to lie, social interactions, and motivation—were more realistic and, more importantly, narrowed down the neural regions activated in the act of deception. Delgado et. al. found that higher ecological tasks recruited the right insular cortex and bilateral anterior cingulate cortex, suggesting that more natural deception engages more specific neural networks rather than confounding signals (Delgado-Herrera, 2021). Identifying high ecological validity tasks that create realistic settings is a key finding, as it will help develop a functional MRI role in deception detection in real-life forensic applications. This discovery also helps evaluate previous studies’ design tasks, which could be enhanced with a high ecological validity design.

Across this review, deception constantly emerges as a fundamentally cognitive process, therefore cognitive-based methods are most appropriate for identifying the specific neural configuration of deception. Foundational neuroimaging data show that the angular gyrus and the inferior frontal gyrus are consistently engaged during deceptive responses, supporting the claim that truth suppression and information manipulation are involved in lying. From this foundation, predictive validity enhancement like dual-goal tuning represents a methodological advancement, as the shift focuses towards improving the validity of fMRI’s ability to detect deception by distinguishing between other closely related social processes.

The work of Lee and colleagues acknowledges the promise and limitations of this approach. Dual-goal tuning seeks to improve the discriminant validity by eliminating overgeneralization; accuracy remains context-dependent, reinforcing concerns about task design. This fact is further acclaimed by Delgado-Herrera and colleagues, whose findings demonstrate that higher ecological validity tasks activate more specific and realistic neural networks involved in deception. Overall, these studies suggest that the future of fMRI deception detection does not lie in a specific neural marker, but in carefully-designed, context-specific paradigms that minimize confounding signals and preserve real-world relevance. At this time, current methods are not yet suitable for direct forensic application; however, with continued enhancement in task-design, predictive modeling, and ecological validity, the prospect of neuroprediction-informed deception detection is increasingly possible.

Deception Detection Technology in Forensics

Forensics is the application of scientific methods and techniques to investigate crime and gather evidence, or to find anything suitable for legal proceedings. Crime and deception intertwine through deception in testimony, suspect interviews, and offender behavior, making deception a methodologically difficult task for forensic analysts to identify. Many have tried, applying their knowledge to create methods and techniques to overcome this challenge; in China circa 1000 BCE, a legal test for deception required individuals to keep dry rice in their mouths—if the rice remained dry after being expelled, the person was judged to be lying. This method was conceived because anxiety and nervousness, believed to be tied to deception, were thought to reduce salivation (Vicianova, 2015). In the 1920s, criminologists invented the polygraph, which tracked respiratory rate, blood pressure changes, and skin reactivity. This machine focused on capturing the subtle physiological changes during deception. Technological advancements have enabled forensic analysts to create more accurate techniques to solve crimes and de-

tect deception. Modern neuroscience technology, like fMRI, allows scientists to capitalize by examining the patterns of activation in the brain linked to deceptive processes. The growth of knowledge permits the development of new methodologies to most accurately detect deception, investigate, gather evidence, and enhance forensic decision-making.

fMRI detection of deception has not yet been labeled as a used and working method in the field of forensics. For this reason, Kozel and colleagues formulated a task design with very high ecological validity, using a “mock sabotage crime paradigm” which simulated a real-life scenario. Researchers randomly assigned participants (“healthy, nonmedicated adults between the ages of 18-50 years”) to two groups: a mock-crime group or a no-crime group. The mock-crime group was instructed to pick up a confidential envelope and steal and destroy a CD containing the video of a convenience store robbery, and admit to picking up the envelope, but not destroying or stealing the CD. The no-crime group did not pick up the envelope or the CD, but were told to lie about picking up the letter. The fMRI results showed 100% sensitivity (ability to detect mock-crime group), but only 33% specificity (ability to detect no-crime group), making fMRI a means of ruling out people in deception detection (Kozel et al., 2022). This study provides a real connection to forensics as it has a high ecological validity task and finds fMRI useful in weeding out suspects with its perfect ability to determine suspects. However, the results are limited by the approximation of their task-design, which cannot equal the level of jeopardy in real-world testing. The inclusion of fMRI’s could be used as a tool to help overcome deception in a forensic study, as it could help weed out suspects, but not as a primary or complete solution.

(Could include study, but it’s saying that fMRI technology makes a juror more prone to a guilty verdict because of confidence in fMRI technology despite not questioning validity— strays away as the technology should not be used if it’s in a courtroom, but no technology would be 100%.)

Conclusion

For thousands of years, deception was viewed as only an observable process, yet modern knowledge and technology are able to discern this concept as being a neural process that must be analyzed through a cognitive lens. fMRI-based neuropsychology, when enhanced by methods like dual-goal tuning, shows greater, in-theory validity than traditional human-observable behavioural patterns. This is not to say fMRI usage is a definitive lie detector, but to acknowledge the valuable use and potential of neural technology in studying deception.

This review highlighted many important findings depicting the past, current, and potential future work of deception detection. DePaulo and colleagues’ study demonstrates that commonly thought behavioural signals of deception really have a weak correlation, and research should look inward. Polygraphs are shown to be unreliable despite their biological approach, measuring other social processes rather than deception. This focus allows work to transition to fMRI and neuropsychology, where accuracy varies as task-design and approach control the validity. fMRI may not be ready for a forensic application, but it shows promise with high ecological validity tasks and an approach to combat overgeneralization like dual-goal tuning.

Deception is best defined as a cognitive process; therefore, to best understand deceptive behaviour, it should be viewed at a

neural level. This is not to state that neuropsychology is entirely correct, however they do address scientific weaknesses in older methods. fMRI technology is not meant to replace ethics and legal judgment, as letting a brain scan decide the truth would be unethical due to its lack of acknowledgment in human comprehension or understanding of morals in the given predicament. This paper seeks to disseminate neuroscience contributions to better the understanding of executive functioning, social processes, and how the brain operates within the confines of deception research, while also evaluating fMRI and its enhancements’ ability to translate to a forensic setting.

Researching a method of detecting deception is inherently flawed, as deception is not a stable neurological or psychological process, but rather a context-dependent behavior. Despite this, researchers have approached the problem using different procedures and methodological frameworks. Even within fMRI research, findings are scattered, as some may use methods like dual-goal tuning to improve overgeneralization, whereas others may not use such techniques and instead search for a deception-specific neural receptor. Across all deception research, combating confounding signals has been the main challenge of identifying deception. It is important to acknowledge the limited diversity in tasks, participant demographics, and types of deception, as most participants were younger adults and were given tasks designed to assess validity under extreme confounding signal conditions. This finite variation in studies makes a plausible forensic connection difficult. It is also important to mention that there are certain aspects of real-world settings that are not fully replicated during testing, like stress and complex circumstances. Additionally, fMRI technology is expensive and not widely accessible.

It is important that research continues on fMRI deception detection, as the work is positive and could be a useful tool in forensic settings. Thus, further research must be conducted on creating efficient task and approach design, which have high ecological validity and have a high chance of overcoming overgeneralization; refinements such as this would make fMRI more accurate and reliable, cutting down its inherent limitations.

References

- Delgado-Herrera, M., Reyes-Aguilar, A., & Giordano, M. (2021). What deception tasks used in the lab really do: Systematic review and meta-analysis of ecological validity of fMRI deception tasks. *Neuroscience*, 468, 88–109. <https://doi.org/10.1016/j.neuroscience.2021.06.005>
- DePaulo, B. M., Lindsay, J. J., Malone, B. E., Muhlenbruck, L., Charlton, K., & Cooper, H. (2003). Cues to deception. *Psychological Bulletin*, 129(1), 74–118. <https://doi.org/10.1037/0033-2909.129.1.74>
- Feng, Y.-J., Hung, S.-M., & Hsieh, P.-J. (2022). Detecting spontaneous deception in the brain. *Human Brain Mapping*, 43(10), 3257–3269. <https://doi.org/10.1002/hbm.25849>
- Kozel, F. A., Johnson, K. A., Grenesko, E. L., Laken, S. J., Kose, S., Lu, X., Pollina, D., Ryan, A., & George, M. S. (2009). Functional MRI detection of deception after committing a mock sabotage crime. *Journal of Forensic Sciences*, 54(1), 220–231. <https://doi.org/10.1111/j.1556-4029.2008.00927.x>

[//doi.org/10.1111/j.1556-4029.2008.00927.x](https://doi.org/10.1111/j.1556-4029.2008.00927.x)

- Lee, S., Niu, R., Zhu, L., Kayser, A. S., & Hsu, M. (2024). Distinguishing deception from its confounds by improving the validity of fMRI-based neural prediction. *Proceedings of the National Academy of Sciences*, 121(50), e2412881121. <https://doi.org/10.1073/pnas.2412881121>
- Lee, S., Niu, R., Zhu, L., Kayser, A. S., & Hsu, M. (2024). Nothing but lies: Improving the validity of neural predictors of deception [Preprint]. *bioRxiv*. <https://doi.org/10.1101/2024.05.08.593230>
- National Research Council. (2003). *The polygraph and lie detection*. National Academies Press. <https://doi.org/10.17226/10420>
- Opancina, V., Sebek, V., & Janjic, V. (2024). Advanced neuroimaging and criminal interrogation in lie detection. *Open Medicine*, 19(1), 20241032. <https://doi.org/10.1515/med-2024-1032>
- Vicianova, M. (2015). Historical techniques of lie detection. *Europe's Journal of Psychology*, 11(3), 522–534. <https://doi.org/10.5964/ejop.v11i3.919>

Medications for Treating REM Sleep Disorders Can Improve Memory Consolidation by Restoring Normal REM Sleep Function

Jianxi Zhou

Abstract: Lack of sleep has become a hidden ailment plaguing modern society, and sleep deprivation can impair memory consolidation. Rapid eye movement (REM) sleep, as a crucial stage of the sleep cycle, is equally important. With the rising number of people suffering from changes in sleep, the lack of REM sleep has become a major and pressing issue. This study aims to investigate whether drug treatment can improve memory impairment caused by REM sleep deprivation and serve to consolidate memories. This paper primarily investigates the effects of treatment with acetylcholine, intraperitoneal ozone, and quinpirole. The study reviews nine research papers focusing on REM sleep, memory consolidation, and medical interventions. By analyzing the collected evidence, the study assessed the extent to which medical interventions can restore REM sleep function and alleviate memory impairments. These findings suggest that medical interventions targeting REM sleep may help alleviate memory impairments caused by sleep deprivation. These findings help us gain a deeper understanding of how to modulate the effects of sleep on memory and lay the groundwork for developing more accessible and effective treatments.

For a long time, sleep has been recognized as a crucial process for consolidating memory, boosting immunity, enhancing cognitive abilities, and promoting cellular metabolism. Therefore, high-quality sleep is essential for maintaining physical and mental health. It eliminates fatigue, repairs brain cells, and helps the body regulate stress and physiological functions during this period (3). Simultaneously, sleep plays a key role in memory consolidation and cognitive function. There are four sleep stages: NREM Stage 1, 2, 3 (N1, N2,

N3) and REM sleep. Among them, rapid eye movement (REM) sleep is particularly vital for hippocampus-dependent memory processing and neural plasticity. The hippocampus is a horseshoe-shaped structure located deep within the temporal lobe of the brain. It serves as a crucial command center responsible for converting short-term experiences into long-term memories and managing spatial navigation. REM sleep typically begins approximately 90 minutes after falling asleep and gradually lengthens toward the end of the sleep cycle. This stage features heightened brain activity, is the primary period for dreaming, and is responsible for memory consolidation, emotional regulation, and knowledge processing. The duration of REM sleep increases as morning approaches because in the early night, the body prioritizes Stage N3 (slow-wave sleep) to repair itself. Once the need for deep sleep is met, the body spends more time in shorter sleep cycles, thereby extending the duration of REM sleep. Consequently, insufficient REM sleep is often a sign or consequence of sleep disorders. Enhancing REM sleep is considered an effective method to mitigate cognitive and memory impairments associated with sleep disturbances.

Research indicates that REM sleep deprivation and related disorders can impair memory consolidation and cognitive performance. REM sleep deprivation refers to a reduction or disruption of REM sleep. Approximately 32.8% of adults in the United States suffer from insufficient sleep, while globally, as many as 45% of the population (about one-third of the total population) suffer from some form of sleep disorder, making sleep disorders a major global health issue. Investigating the neurological consequences and interventions for disrupted REM sleep has become a critical research domain.

Research indicates that various medications and therapeutic approaches can increase REM sleep cycles to varying degrees, thereby mitigating memory impairment caused by sleep disorders. These interventions may even counteract sleep disturbances associated with certain neurological diseases, such as seizures. The reduction in epileptic activity during REM sleep is thought to be caused by EEG desynchronization, mediated primarily by cholinergic neurotransmission (5). This review aims to examine medical interventions targeting REM sleep disorders, focusing on restoring normal REM sleep function and enhancing memory consolidation capacity.

REM sleep is the sleep stage during which paradoxical sleep occurs. It is characterized by random eye movements and muscle tone suppression, and plays a role in memory processing (9). Evidence indicates that both non-rapid eye movement (NREM) and REM sleep contribute to memory consolidation. Theoretical frameworks such as the active systems consolidation hypothesis and synaptic homeostasis hypothesis further emphasize the important role of sleep—particularly NREM-related oscillatory activity—in regulating memory consolidation processes (2). The active consolidation hypothesis posits that memories are initially encoded in the hippocampus and are actively “transferred” or replayed to the neocortex during sleep for long-term, stable storage. The synaptic homeostasis hypothesis (SHY) suggests that sleep reduces the overall synaptic strength that becomes oversaturated during daytime learning, thereby restoring energy balance and improving the signal-to-noise ratio to facilitate better recall. Both hypotheses emphasize the role of sleep in memory consolidation. Among these, declarative memory relies more heavily on NREM sleep, while procedural memory—involving motor skills and learned behaviors—is more dependent on REM sleep (1). Declarative

memory refers to the conscious, explicit recall of facts, events, and specific knowledge. It relies on the medial temporal lobe, including the hippocampus. Procedural memory is responsible for mastering how to perform actions, habits, and skills without conscious thought. Unlike declarative memory, which relies on the medial temporal lobe, procedural memory depends on the basal ganglia, the cerebellum, and the motor cortex. This suggests that REM sleep plays a unique role in consolidating specific types of memory, particularly those related to learned behaviors.

Previous studies indicate that REM sleep plays a crucial role in memory consolidation. Hyndych reviews that sleep supports long-term memory consolidation by reactivating hippocampal memory traces and redistributing them to neocortical regions, thereby strengthening synaptic connections involved in recent learning (1). This suggests that interactions between the hippocampus and neocortex during sleep constitute a mechanism for enhancing memory.

REM sleep plays a crucial role in processing emotional memories. Research has found that higher average percentages or efficiency of REM sleep over four consecutive nights correlate with fewer intrusive memories reported over the following three days (4). This suggests that REM sleep helps protect individuals from being troubled by intrusive memories. Additionally, it was discovered that longer average total sleep duration over four nights also leads to fewer reported intrusive memories over three days (4). Therefore, even simply increasing sleep duration can reduce intrusive memories and alleviate the stress these memories place on the brain.

Research indicates that REM sleep also plays an indispensable role in higher cognitive functions such as executive function. Executive function refers to a set of mental processes controlled by the prefrontal cortex of the brain. It enables individuals to plan, focus their attention, and regulate their emotions. Hyndych indicates that the prefrontal cortex is a key region for executive function, and its activity undergoes dynamic changes during sleep. During slow-wave sleep, activity in the prefrontal cortex decreases. Specifically, slow-wave sleep (SWS) is the deepest stage of NREM sleep, characterized by slow, high-amplitude brain waves (delta waves) and reduced metabolic activity in the brain. Conversely, during REM sleep, activation in the limbic system and parahippocampal structures increases (1). This reflects the distinct role of REM sleep in regulating brain function compared to NREM sleep. REM sleep plays a crucial role in emotional regulation, memory consolidation, and brain development. This is primarily because the forebrain and cortex are highly active during REM sleep, contributing to vivid dream imagery and emotional processing. In contrast, SWS focuses more on physical recovery and reduced metabolic activity than REM sleep, as activity in the prefrontal cortex decreases during this phase.

REM sleep facilitates memory consolidation and cognitive processing, whereas REM sleep disruption produces opposite effects. Animal studies consistently demonstrate that REM sleep deprivation impairs learning, memory retention, and neural processes associated with memory consolidation.

The Morris water maze (MWM) task was employed to assess spatial learning and memory abilities in rats. The sleep-deprived group (SD group) exhibited significantly prolonged escape latency on day 4 ($P < 0.05$), indicating that REM sleep deprivation impairs spatial memory in rats. Concurrently, the SD group showed markedly increased glial cell density surrounding neu-

rons in the hippocampus and prefrontal cortex. Neurons exhibited degenerative changes characterized by nuclear condensation and partial liquefactive necrosis. Nuclear condensation, also known as nuclear compaction, refers to the irreversible condensation of chromatin within the cell nucleus during cell necrosis or apoptosis. Liquefactive necrosis, meanwhile, is a type of tissue death. Both processes represent the final stages of cell death, characterized by a significant loss of neuronal connections, which leads to cognitive impairment. Furthermore, neuronal damage appeared in the rat locus coeruleus and amygdala (6). This indicates that the impact of REM sleep deprivation on memory extends beyond observable behavioral differences to include internal neuronal damage and structural alterations.

Subsequently, it was found that most mice exhibited prolonged reaction times, with some unable to complete the task. Additionally, mice were unable to locate the platform position. Dr. Perla Ugalde-Muñiz demonstrated that three consecutive days of REM sleep deprivation impaired object acquisition and memory retrieval in mice, even after they had mastered the task and become familiar with it (8). This indicates that REM sleep deprivation not only affects memory formation but also diminishes the ability to recall existing memories.

Perla Ugalde-Muñiz highlighted a close association between pro-inflammatory cytokines and cognitive function during RSD. Consequently, spatial memory deficits likely stem from neuroinflammation in the hippocampus. This underscores how intrinsic cellular structures disrupted by REM sleep deprivation affect cognition and memory, thereby impairing spatial memory in mice.

Anna Hyndych's review highlights that sleep deprivation heightens amygdala reactivity, weakens frontocortical-amygdala connectivity, and leads to emotional disturbances, impulsivity, and risk-taking behaviors. Sleep deprivation not only impairs memory but also plays a critical role in daily behavior (1). Research shows that deprivation of REM sleep impairs spatial memory and memory retrieval, resulting not only in reduced memory capacity but also in the loss of previously acquired memories. These manifestations are not merely behavioral but also involve structural changes in the nervous system.

Given that sleep deprivation during REM sleep impairs memory consolidation and cognitive function, researchers have begun to explore whether medical interventions can restore REM sleep and thereby alleviate these impairments. To date, researchers have investigated various medications and therapeutic approaches to assess their potential to modulate REM sleep and improve memory-related outcomes. Among these methods, studies have examined D2 dopamine receptor-targeted therapies and the effects of long-term intraperitoneal ozone administration on REM sleep architecture and memory function. This section summarizes the therapeutic approaches involving these agents that can improve REM sleep architecture and thereby alter memory consolidation.

Experimental data have fully demonstrated the role of cholinergic mechanisms in the formation of long-term memory, as well as the role played by interactions between the hippocampus, entorhinal cortex, and the cortex. Cholinergic mechanisms serve as a fundamental pathway that transmits neural signals from the skin to the central nervous system, connecting virtually all sensory systems. Yiyao Zhang claimed that optogenetic enhancement of cholinergic activity leads to memory delays, thereby impairing memory performance (7).

YiNing Yan demonstrated through experiments that intraperitoneal injection of ozone, a medical procedure in which a mixture of oxygen and ozone is injected into the abdomen, can reverse spatial learning and memory deficits associated with REM sleep deprivation. The study employed a modified multi-platform model for REM sleep deprivation and the Morris water maze. In the Morris water maze test, the number of crossings in the sleep-deprived group (SD group) was significantly lower than that in the control group. The number of crossings in the ozone group was significantly higher than that in the SD group ($P < 0.05$). This indicates that ozone can prevent sleep deprivation-induced learning and memory impairments. It highlights that ozone can mitigate sleep deprivation-induced memory deficits.

The study also found that the underlying changes causing memory deficits might be due to alterations in gene expression in the hippocampus; therefore, the *Sema3A* gene was selected for further qPCR analysis. The results showed that, compared with the control group, *Sema3A* expression was significantly upregulated in the SD group; conversely, compared with the SD group, *Sema3A* expression was downregulated in the ozone group (6). This suggests that the downregulation of *Sema3A* expression following intraperitoneal ozone administration may contribute to the prevention of spatial learning and memory impairments caused by REM sleep deprivation.

In addition to intraperitoneal injection and acetylcholine, studies have also found that quinpirole (QUIN), which is a psychoactive research chemical and drug that acts as a selective dopamine D2 and D3 receptor agonist, can improve episodic memory impairments caused by REM sleep deprivation. Perla Ugalde-Muñiz found that continuous administration of quinpirole during 3 days of REM sleep deprivation (RSD) and following the training period significantly reversed the cognitive impairments induced by RSD. Mice treated with QUIN spent less time in the target quadrant than the control group. These data suggest that QUIN mitigates the damage caused by sleep deprivation. Furthermore, the movement trajectories of the QUIN-treated group resembled those of the control mice, indicating that QUIN treatment can reverse the damage caused by sleep deprivation, bringing the mice closer to normal behavior.

This article reviews medical interventions for REM sleep disorders that can restore and improve memory consolidation processes impaired by sleep deprivation. We focus on experimental interventions targeting REM sleep administered to sleep-deprived mice and examine how sleep deprivation and memory status affect these interventions. The results indicate that REM sleep promotes memory consolidation, including spatial and learning memories, by activating the limbic system and parahippocampal structures. REM sleep deprivation (i.e., reduced REM sleep) weakens the connectivity between the prefrontal cortex and the amygdala, thereby impairing memory function. Consequently, we found that certain therapeutic interventions can restore REM sleep and improve short-term memory (although it remains unclear whether they improve long-term memory). The study found that three therapeutic approaches—acetylcholine, intraperitoneal ozone, and quinpirole—all mitigated the damage caused by sleep deprivation to some extent.

These findings are significant because they highlight the critical role that REM sleep plays in maintaining cognitive function and suggest that REM sleep deprivation may lead to neurological and psychological dysfunction. Given that a large proportion of the

global population suffers from sleep disorders, the implications of disrupted REM sleep warrant further investigation into its potential effects on daily learning, decision-making, and emotional regulation.

Furthermore, findings on therapeutic interventions such as acetylcholine, intraperitoneal ozone, and quinpirole suggest potential avenues for alleviating sleep-deprivation-related cognitive deficits. These treatments suggest that interventions targeting REM sleep may not only restore normal sleep architecture but also improve memory-related outcomes, offering promising insights for the clinical management of sleep disorders and related neurological conditions.

However, the research still has several limitations. The studies included in this review all used animal models, which cannot fully reflect human neurophysiological processes. Furthermore, while the studies observed improvements in short-term memory, it remains unclear whether these interventions have the same effect on long-term memory. Future studies could aim to translate these findings into research, particularly human studies, and further investigate the long-term effects of REM sleep interventions on memory and cognitive function. Understanding these mechanisms will aid in the development of more effective treatments for sleep disorders and improve overall brain health.

Beyond memory consolidation, REM sleep may also play a protective role in neurological disorders. For instance, studies on seizures indicate that REM sleep can suppress abnormal neural activity; conversely, sleep fragmentation and disruptions to slow-wave sleep may exacerbate seizures. (5) This highlights the broader clinical significance of REM sleep—extending beyond its role in memory function—and suggests its potential therapeutic value in the context of neurological disorders.

References

- Hyndych, A., El-Abassi, R., & Mader, E. C., Jr. (2025). The Role of Sleep and the Effects of Sleep Loss on Cognitive, Affective, and Behavioral Processes. *Cureus*, 17(5), e84232. <https://doi.org/10.7759/cureus.84232>
- Lutz, N. D., Harkotte, M., & Born, J. (2026). Sleep's contribution to memory formation. *Physiological reviews*, 106(1), 363–483. <https://doi.org/10.1152/physrev.00054.2024>
- Eugene, A. R., & Masiak, J. (2015). The Neuroprotective Aspects of Sleep. *MEDtube science*, 3(1), 35–40.
- Alkalame, L., Ogden, J., Clark, J. W., Porcheret, K., Risbrough, V. B., & Drummond, S. P. A. (2024). The relationship between REM sleep prior to analog trauma and intrusive memories. *Sleep*, 47(12), zsae203. <https://doi.org/10.1093/sleep/zsae203>
- Frauscher, B., & Timofeev, I. (2024). Seizures and Sleep. In J. L. Noebels (Eds.) et. al., *Jasper's Basic Mechanisms of the Epilepsies*. (5th ed., pp. 279–296). Oxford University Press. <https://doi.org/10.1093/med/9780197549469.003.0014>
- Yan, Y. N., Williams, J. P., Niu, K., Zhang, W. H., Zhang, J. F., Shi, L., & An, J. X. (2022). Intraperitoneal ozone injection prevents REM sleep deprivation - induced spatial learning and memory deficits by suppressing the expression of *Sema3A* in the hippocampus in rats. *Iranian journal of basic medical sciences*, 25(8), 980–988. <https://doi.org/10.22038/IJBMS.2022.63994.14112>
- Zhang, Y., Cao, L., Varga, V., Jing, M., Karadas, M., Li, Y., &

- Buzsáki, G. (2021). Cholinergic suppression of hippocampal sharp-wave ripples impairs working memory. *Proceedings of the National Academy of Sciences of the United States of America*, 118(15), e2016432118. <https://doi.org/10.1073/pnas.2016432118>
8. Ugalde-Muñiz P, Hernández-Luna MG, García-Velasco S, Lugo-Huitrón R, Murcia-Ramírez J, Martínez-Tapia RJ, Noriega-Navarro R, Navarro L. Activation of dopamine D2 receptors attenuates neuroinflammation and ameliorates the memory impairment induced by rapid eye movement sleep deprivation in a murine model. *Front Neurosci*. 2022 Oct 5;16:988167. doi: 10.3389/fnins.2022.988167. PMID: 36278007; PMCID: PMC9579422.
9. Yamada, R. G., & Ueda, H. R. (2020). Molecular mechanisms of REM sleep. *Frontiers in Neuroscience*, 13, 1402.

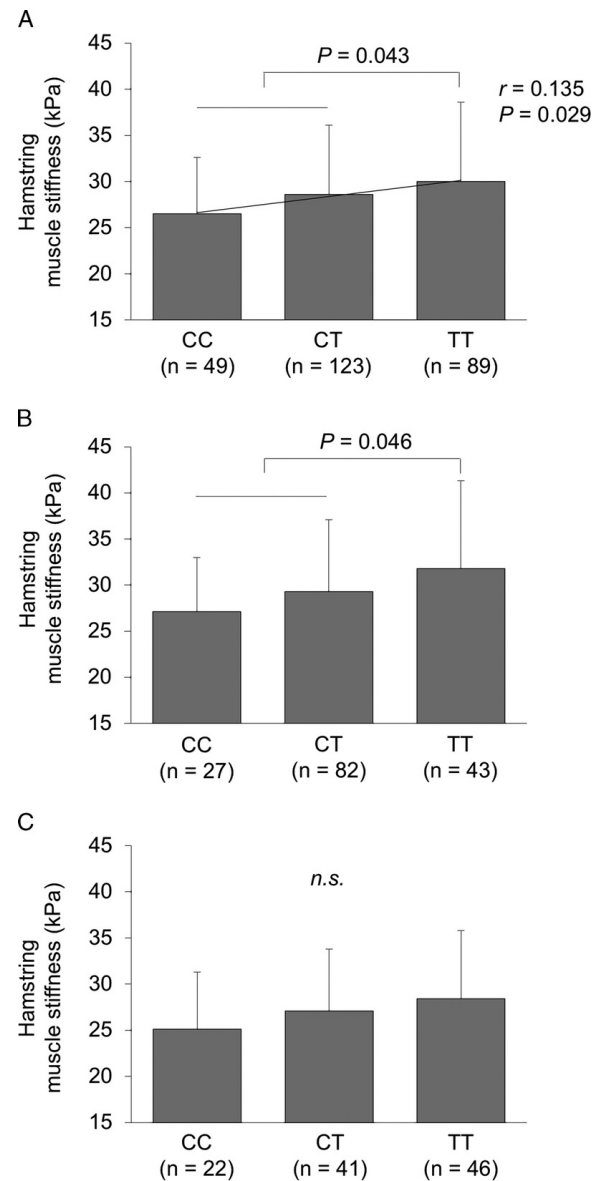


Figure 3. Correlating hamstring stiffness with PCR-ESR1 variant allele type. From “Kumagai, H., Miyamoto-Mikami, E., Hirata, K., Kikuchi, N., Kamiya, N., Hoshikawa, S., Zempo, H., Naito, H., Miyamoto, N., & Fuku, N. (2019). ESR1 rs2234693 Polymorphism Is Associated with Muscle Injury and Muscle Stiffness. *Medicine and science in sports and exercise*, 51(1), 19–26. <https://doi.org/10.1249/MSS.0000000000001750>”

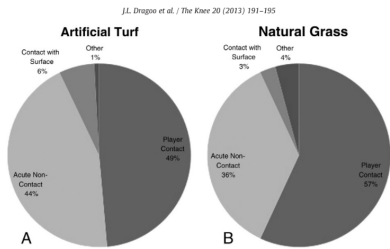


Figure 4. Incidence of ACL Injuries on Artificial Turf. From “Dragoo, J. L., Braun, H. J., & Harris, A. H. (2013). The Effect of Playing Surface on the Incidence of ACL Injuries in National Collegiate Athletic Association American Football. *The Knee*, 20(3), 191–195. <https://doi.org/10.1016/j.knee.2012.07.006>”

TABLE 1
Basic Components of the PEP Program^a

1. Warm-up (50 yards each):
 - A. Jog line to line of soccer field (cone to cone)
 - B. Shuttle run (side to side)
 - C. Backward running
2. Stretching (30 s × 2 reps each):
 - A. Calf stretch
 - B. Quadricep stretch
 - C. Figure 4 hamstring stretch
 - D. Inner thigh stretch
 - E. Hip flexor stretch
3. Strengthening:
 - A. Walking lunges (20 yards × 2 sets)
 - B. Russian hamstring (3 sets × 10 reps)
 - C. Single toe-raises (30 reps on each side)
4. Plyometrics (20 reps each):
 - A. Lateral hops over 2 to 6 inch cone
 - B. Forward/backward hops over 2 to 6 inch cone
 - C. Single leg hops over 2 to 6 inch cone
 - D. Vertical jumps with headers
 - E. Scissors jump
5. Agilities:
 - A. Shuttle run with forward/backward running (40 yards)
 - B. Diagonal runs (40 yards)
 - C. Bounding run (45–50 yards)

Figure 5. Ideal Warm-Up Program to Reduce ACL Injury Risk in Female Athletes. From “Gilchrist, J., Mandelbaum, B. R., Melancon, H., Ryan, G. W., Silvers, H. J., Griffin, L. Y., Watanabe, D. S., Dick, R. W., & Dvorak, J. (2008). A randomized controlled trial to prevent noncontact anterior cruciate ligament injury in female collegiate soccer players. *The American journal of sports medicine*, 36(8), 1476–1483. <https://doi.org/10.1177/0363546508318188>”

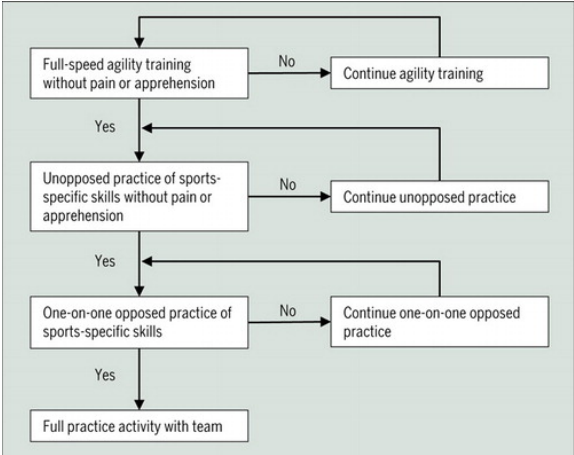


Figure 6. Suggested Return-to-Sport Criteria for Female Athletes Following ACL Tear. From “Posthumus, M., September, A. V., O’Cuinneagain, D., van der Merwe, W., Schwellnus, M. P., & Collins, M. (2010). The association between the COL12A1 gene and anterior cruciate ligament ruptures. *British journal of sports medicine*, 44(16), 1160–1165. <https://doi.org/10.1136/bjsm.2009.060756>”