A Systematic Review of Etiological Risk Factors Associated With Early Mortality Among National Football League Players

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Background: Multiple risks predispose professional football players to adverse health outcomes and, in extreme cases, early death; however, our understanding of etiological risk factors related to early mortality is limited.

Purpose: To identify etiological risk factors associated with all-cause and cause-specific mortality among National Football League (NFL) players.

Study Design: Systematic review; Level of evidence, 3.

Methods: Articles examining all-cause and cause-specific mortality risk factors among previous NFL players were identified by systematically searching: PubMed, PsycINFO, Web of Science, and Google Scholar from 1990 to 2017. Study eligibility and quality were evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results: A total of 801 nonduplicated studies were identified through our search strategy. Of these, 9 studies examining 11 different risk factors were included in the systematic review. Overall, the risk of all-cause and cause-specific mortality was lower among NFL players than among the general male population in the United States. Nonwhite athletes, those in power positions, and those with a high playing-time body mass index ($\geq$30 kg/m^2) were associated with elevated all-cause and cardiovascular mortality risks.

Conclusion: Methodological issues associated with the examined all-cause and cause-specific mortality risk factors preclude a definitive conclusion of etiological protective or risk effects. Comparison groups less prone to selection bias ("healthy worker effect") and a life-course approach to the evaluation of suspected risk factors are warranted to identify etiological factors associated with early mortality among NFL players.

Keywords: National Football League; NFL; early mortality; etiological; risk factors

Multiple risks predispose professional football players to adverse health outcomes[15,24,35] and, in extreme cases, early death[1-3,14,16-19,36]; however, our understanding of etiological risk factors associated with early mortality is limited. It is postulated that multiple pathways moderated by National Football League (NFL) player attributes and game-exposures are associated with longevity.[1-3,14,16,17,19,24,36] Existing evidence, however, is limited by a number of methodological issues (eg, the "healthy worker effect," misclassified latency periods, and suspected confounding effects). The delineation of etiological risk factors related to early mortality among NFL players is further complicated by competing outcomes such as cardiovascular mortality, catastrophic injuries, and mental health–related mortality.

Cardiovascular mortality is often a concern among certain playing positions, specifically linemen. Linemen tend to have a higher playing-time body mass index (BMI), which is a risk factor for cardiovascular mortality among the general population.[6] However, it is unclear if a higher playing-time BMI directly translates to an increased risk of cardiovascular mortality among NFL players. This is underlined by studies indicating that BMI overestimates

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adiposity[28] (a prognostic factor for cardiovascular disease risk) among athletes with a large muscle mass. Moreover, BMI after an athlete's NFL career changes differentially by player position.[27] In some regard, the recent decline in cardiovascular mortality among NFL players,[3] attributed to preventive efforts (health promotion) initiated in the late 1990s,[35] lends weight to the notion of temporal programming of risk during and after a player's career. However, the influences of life-course BMI or adiposity trajectory changes on the cardiovascular risk and mortality are yet to be examined among NFL players.

Football is a contact sport with an elevated incidence of high-impact collisions that can result in catastrophic injuries. Some studies have suggested that physically elite people, through appropriate training-based fitness, can develop physical capacities that protect against injury risk.[13] On the other hand, repeated concussive and subconcussive blows to a player's head and body are linked to chronic traumatic encephalopathy (CTE) and other neurodegenerative diseases.[16,17,22] Mediated by impaired decision making,[21,33] mental health disorders (eg, depression),[21] and substance and alcohol abuse,[9] football-related physical trauma is suspected to result in early death among NFL players. However, mediation analyses to confirm these relationships are lacking. Although there is a growing recognition of the link between mental health problems and CTE among athletes exposed to repeated traumatic injuries, the case selection in CTE studies is suspect to volunteer-related bias, and a relatively small percentage of deceased NFL player brains have been examined to date.[21,22]

Overall, it is unclear whether NFL players are at an increased risk of early mortality from factors associated with football. Therefore, the objective of this study was to identify etiological risk factors associated with all-cause and cause-specific mortality among NFL players. We also discuss study findings in the context of epidemiological validity and provide recommendations for future research.

METHODS

Data Sources and Searches

We conducted systematic searches of the existing literature to gather valid information on risk factors associated with mortality among NFL players. Specifically, we searched 3 electronic databases—PubMed, PsycINFO, and Web of Science—for articles published from January 1, 1990, to December 31, 2017. We also searched Google Scholar, previous systematic reviews, and selected study bibliographies for additional articles. The search strategy included the use of combinations of the following keywords for the (1) population of interest (NFL players): pro-football, athletes, elite, sports, players, football players; (2) outcome of interest (mortality): mortality, all-cause mortality, cause-specific mortality, longevity, death, life expectancy, fatal injuries; and (3) risk factors: exposures, risk, risk factors, mediators, moderators. The search results were limited to English-language text.

### Study Eligibility, Selection, and Qualitative Assessment

We conducted the search strategy in 3 phases. In phase 1, we screened all documents retrieved based on title and abstract (A.H.O., B.L.K., B.W., and S.S.). Two exclusion criteria in phase 1 were (1) studies not related to American football and (2) no original data. The full text of articles moved to phase 2 were reviewed by A.H.O. and B.L.K. to determine their eligibility. Eligible articles were those that examined (1) NFL populations, (2) mortality outcomes, and (3) risk factor measures of association. We excluded case series and reports. We entered data from all articles moved to phase 3 into standardized electronic forms developed in Microsoft Access. The data included study characteristics (design, geographic location, period, and duration of the study), participant selection, and ascertainment of outcomes and exposures (risk factors). In phase 3, A.H.O. and B.L.K. independently evaluated articles for their epidemiological quality. The authors (A.H.O. and B.L.K.) assessed 8 signaling questions informed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to summarize 5 quality domains relevant to observational studies: participant selection, prognostic/confounding factors, cointervening exposure, exposure assessment, and outcome assessment. We summarized each domain with a rating of low, moderate, or high risk of bias. We assigned studies with a low risk of bias across all 5 domains with a "good" overall quality rating. Studies with ≥1 moderate- and high-risk ratings were assigned a "fair" and "poor" overall quality rating, respectively. Disagreements or uncertainties were resolved through discussion with B.W. and S.S.

Operational Definitions of Mortality

In this study, all-cause and cause-specific mortality outcomes examined among reviewed studies were limited to those verified using the National Death Index (NDI) initiated in 1979. The NDI provides causes of death coded to the International Classification of Diseases (ICD) in effect at the time of death. In cases in which the NDI was not used, we considered studies and/or mortality outcomes that were verified using death certificates from state vital statistics offices and/or coded by a certified nosologist. Cardiovascular-related mortality was defined based on the ICD-10 classification codes 100 through 178. Catastrophic injury–related deaths were defined as those that occurred during or after a player's NFL career that were linked to a severe injury to the spine, spinal cord, skull, or brain.

Summary Measures of Mortality Risk Factor Associations

The following mortality (or longevity) risk measures of association were examined in the selected studies: hazard ratio (HR) of death, life expectancy, standardized mortality ratio (SMR), standardized rate ratio (SRR), standardized
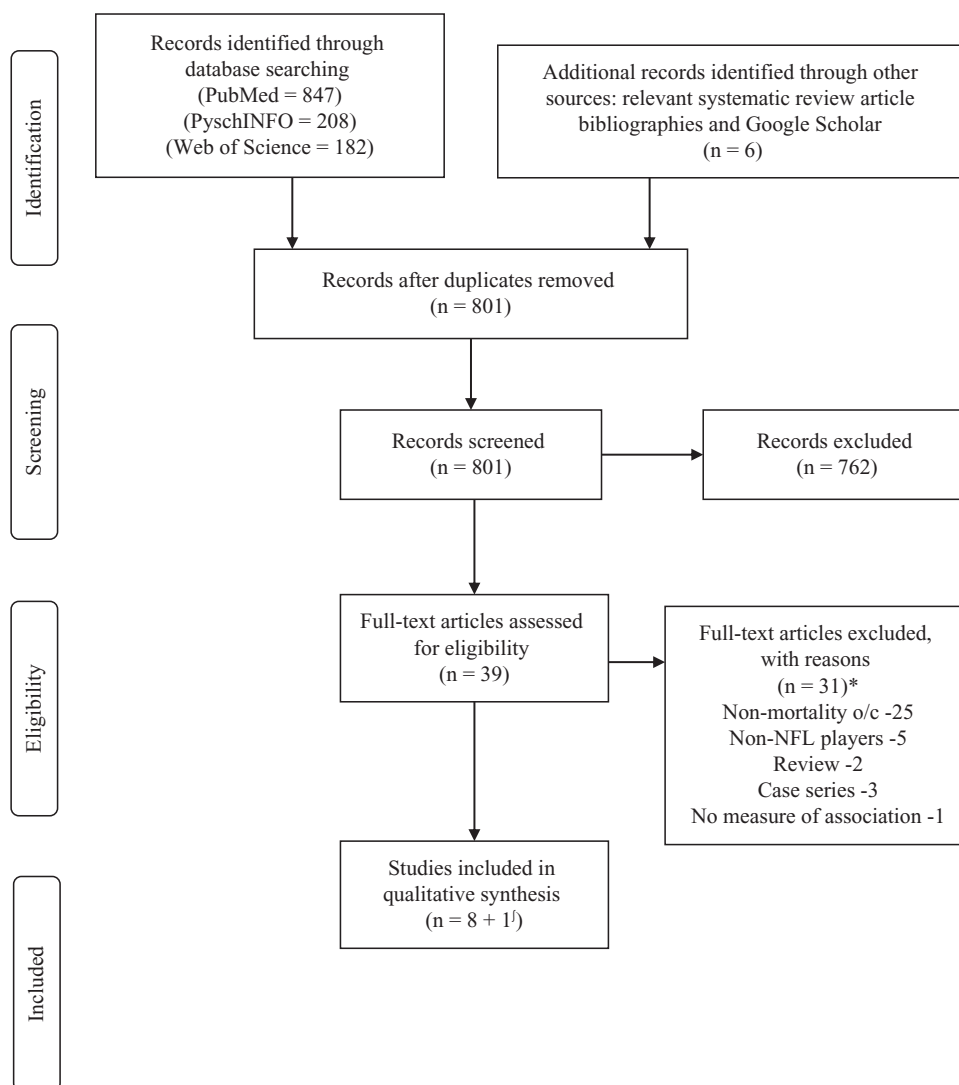
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the literature search and study selection process. *Some studies met more than 1 exclusion criterion. [∫]A recently published study[36] was not identified through our study search strategy. NFL, National Football League; o/c, outcomes.

proportional mortality ratio, mortality rate, mortality odds ratio (OR), and regression and correlation coefficients.

RESULTS

Summary of Reviewed Studies

We identified 801 nonduplicated studies through the search strategy, of which 39 (5%) were eligible for review in phase 2. Of the 39 studies reviewed in phase 2, we excluded 25 studies because of a lack of mortality outcomes, 5 studies exclusively examined non-NFL players, 2 studies were review studies, 3 studies were case series/reports, and 1 study did not report any mortality risk measures of association (Figure 1). Table 1 summarizes the study character-istics of the 8 articles considered in phase 3 (data extraction and quality assessment). We also included results from a

recent study by Venkataramani et al[36] that examined the association between NFL career participation and the mor-tality risk in retirement. Table 2 provides a summary of study-specific epidemiological quality ratings. Briefly, all the articles had a "poor" overall quality rating but were deemed acceptable for a quantitative evaluation.

All-Cause Mortality

Seven cohort studies (Appendix Table A1) examined 5 risk factors (being an NFL player, player position, length of career, race/ethnicity, and playing-time BMI) associated with all-cause mortality among previous NFL players in 6 cohorts: <1940,[1] 1959-1988,[2,3,16,17] 1970 and 1994,[14] 1986-2012,[19] and 1982-1992.[36] Overall, the risk of all-cause mortality was lower among NFL players than among the general population of men in the United

TABLE 1
Summary Characteristics of Studies Reviewed That Examine
Mortality Risk Factors Among NFL Players[a]

Author (Year)	Study Design (Sample Size)	Playing Period	Demographics	Inclusion/Exclusion	Adverse Outcome(s)	Risk Factors Examined
Baron et al[3] (2012)	Retrospective cohort (n = 3439)	1959-1988	Race (white: 60%; black: 39%); age at first season: median, 22 y (range, 19-34 y)	Retired NFL players with >5 pension-credited playing seasons in 1959-1988	All-cause and cause-specific mortality	NFL player (vs US men), player position, race, and BMI (adjusted confounders: race and age)
Abel and Kruger[1] (2006)	Retrospective cohort (n = 1512)	<1940		Deceased NFL players who debuted before 1940	Death	Years played, player position, and BMI
Baron and Rinsky[2] (1994)	Retrospective cohort (n = 6848)	1959-1988	Race (white: 54%); age at first season: mean, 23 y	Retired NFL players with >5 pension-credited playing seasons in 1959-1988	All-cause and cause-specific mortality	NFL player (vs US men), player position, race, and BMI
McKee et al[23] (2013)	Case control (n = 35)	NR	Age at death: mean, 67 ± 17 y (range, 38-98 y)	Deceased NFL players with brains donated to Boston University	Neuropathological diagnoses	Player position
Lehman et al[17] (2016)	Retrospective cohort (n = 3439)	1959-1988	Race (white: 60%; black: 39%); age at first season: median, 22 y (range, 19-34 y)	Retired NFL players with >5 pension-credited playing seasons in 1959-1988	Suicide	NFL player (vs US men), player position (speed vs nonspeed),[b] race, and BMI
Lehman et al[16] (2012)	Retrospective cohort (n = 3439)	1959-1988	Race (white: 60%; black: 39%); age at first season: median, 22 y (range, 19-34 y)	Retired NFL players with >5 pension-credited playing seasons in 1959-1988	All-cause and cause-specific mortality	NFL player (vs US men)
Lincoln et al[19] (2018)	Retrospective cohort (n = 9778)	1986-2012	Race (white: 33%; black: 65%; other: 3%); age at death: median, 38 y (range, 23-61 y); age while alive: median, 41 y (range, 24-68 y)	At least 1 year in the NFL with a last season in 1986-2012	All-cause and cause-specific mortality	NFL player (vs US men), player position, race, and BMI
Koning et al[14] (2014)	Retrospective cohort (1970: n = 1244; 1994: n = 1600)	1970 and 1994	1970: Race (white: 65%); mean age, 25 y 1994: Race (white: 34%); mean age, 26 y	Played at least 1 game during the 1970 and 1994 seasons	All-cause mortality	No. of games played, position, and race/ethnicity
Venkataramani et al[36] (2018)	Retrospective cohort (n = 3812)	1982-1992	Race (NR); age at first season: mean, 23 ± 2 y; playing-time BMI: mean, 30 ± 4 kg/m^2	Retired NFL players who debuted in 1982-1992; kickers, punters, and players who died before retirement were excluded	All-cause and cause-specific mortality	Career players (vs replacement players), birth year, playing-time BMI, height (last NFL year), and position

[a]BMI, body mass index; NFL, National Football League; NR, not reported; US, United States.
[b]Speed position: quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker. Nonspeed position: defensive and offensive linemen. Excluded: punters and kickers.

States (US), even after adjusting for differences in the length of players' career in years (SMR range, 0.42-0.60), position (SMR range, 0.22-0.72), playing-time BMI (SMR range, 0.31-1.12), and race/ethnicity (SMR range, 0.39-0.63).[3,14,19]

Among NFL players, Lincoln et al[19] showed that power positions (vs speed: SMR, 2.16 [95% CI, 1.62-2.86]), nonwhite race (vs white: SMR, 1.63 [95% CI, 1.21-2.21]), and higher playing-time BMI (vs <30 kg/m^2: 30-34 kg/m^2 :

SMR, 1.51 [95% CI, 1.10-2.06] and ≥35 kg/m^2: SMR, 3.84 [95% CI, 2.66-5.54]) were associated with a higher risk of early mortality. Similar results were reported by Koning et al[14] for race and player position among NFL players who played during the 1970 season (but not among those who played during the 1994 season). Conversely, for BMI, Abel and Kruger[1] showed a reversed relationship: a higher BMI was associated with a lower risk of mortality. In addition, Abel and Kruger[1] found that increased longevity was

TABLE 2
Risk of Bias Assessment for Selected Studies That Examine Mortality Risk Factors Among NFL Players[a]

Author (Year)	Study Design (Sample Size)	Selection Bias	Exposure Assessment Bias	Prognostic/ Confounding Bias	Outcome Assessment Bias	Cointervening Exposure Bias
Baron et al[3] (2012)[b]	Retrospective cohort (n = 3439)	Low risk	Low risk	High risk	Low risk	Low risk
Abel and Kruger[1] (2006)[c]	Retrospective cohort (n = 1512)	High risk	High risk	High risk	Moderate risk	High risk
Baron and Rinsky[2] (1994)[d]	Retrospective cohort (n = 6848)	High risk	High risk	High risk	Low risk	High risk
Lehman et al[16] (2012)[e]	Retrospective cohort (n = 3439)	Low risk	Low risk	High risk	Low risk	Low risk
Lehman et al[17] (2016)[f]	Retrospective cohort (n = 3439)	Low risk	Low risk	High risk	Low risk	Low risk
Lincoln et al[19] (2018)[d]	Retrospective cohort (n = 9778)	High risk	High risk	High risk	Low risk	High risk
McKee et al[23] (2013)[e]	Case control (n = 35)	Low risk	Low risk	High risk	Low risk	High risk
Koning et al[14] (2014)[c]	Retrospective cohort (1970: n = 1244; 1994: n = 1600)	High risk	High risk	High risk	High risk	High risk
Venkataramani et al[36] (2018)[c]	Retrospective cohort (n = 3812)	Low risk	High risk	High risk	Low risk	High risk

[a]NFL, National Football League.
[b]Cardiovascular mortality.
[c]All-cause mortality.
[d]All-cause and cause-specific mortality.
[e]Neurodegenerative-related mortality.
[f]Suicide.

associated with longer playing careers, while Lincoln et al[19] did not. Koning et al[14] also reported no association ($P = .60$) between career length and mortality in a comparable reference period (1994 season) but found an elevated mortality risk (HR, 4.47; $P = .01$), with more games played at an earlier reference period (1970 season). Venkataramani et al[36] showed that the mortality risk was not different between NFL career and replacement players who participated in the NFL during a 3-game league-wide player strike in 1987, even after adjusting for differences in player position, playing-time BMI, and height (HR, 1.38 [95% CI, 0.95-1.99]).

Cardiovascular Mortality

Four cohort studies (Appendix Table A2) examined 6 cardiovascular mortality risk factors: being an NFL player, player position, length of career, race/ethnicity, playing-time BMI, and reference period.[2,3,16,19] Similar to overall mortality, irrespective of age, position, and race/ethnicity, the risk of cardiovascular mortality was lower among NFL players compared with US men (SMR range, 0.68-0.71).[2,3,16,19] An NFL player follow-up that occurred in 2000 or after was associated with a 72% lower risk of cardiovascular mortality (HR, 0.28 [95% CI, 0.12-0.71]) than an earlier follow-up that occurred before 1980.[3] Among NFL players, high (≥30 kg/m^2) playing-time BMI (SRR range, 3.90-9.03), nonwhite race/ethnicity (HR, 1.57 [95% CI, 1.15-2.55][3] and OR, 1.70 [95% CI, 1.01-2.98][2]), and power positions (SRR range, 2.12-2.99) were associated with an increased risk of cardiovascular mortality.[2,3,19]

Catastrophic Injuries

For catastrophic injury–related mortality, 4 cohort studies (Appendix Tables A3-A5) examined 3 risk factors: being an

NFL player, and player position.[16,17,19,23] Overall, NFL players had a lower risk (SMR range, 0.63-0.69) of injury-related death than the general population of US men, irrespective of position played or race/ethnicity.[16,19] However, neurodegenerative causes of death (eg, dementia/Alzheimer disease and amyotrophic lateral sclerosis), also linked to a player's NFL career, were higher among speed position players (ie, fullback/halfback/defensive back/running back/ quarterback, linebacker, tight end, and wide receiver positions: SRR, 4.74 [95% CI, 2.59-7.95]) than US men.[16]

Conversely, Lehman et al[16] showed that the risk of brain- and nervous system–related deaths was not different among NFL players versus US men (SMR range, 2.83-3.26). A case-control study conducted by McKee et al[23] showed that career length ($P < .01$), years since retirement ($P < .01$), and age at death ($P < .01$) were positively correlated with a pathological stage of CTE. Their study did not find an association between family-reported numbers of concussions, years of education, lifetime steroid use, player position, *APOE* e4 allele gene, and stage of CTE ($P > .05$).

Although not proximately related to football injuries, the mortality risk associated with violence (SMR, 0.27 [95% CI, 0.14-0.46])[16] and suicide (SMR, 0.47 [95% CI, 0.24-0.82])[17] was lower among NFL players than US men. Among NFL players, there was no difference in the mortality risk between speed and nonspeed position players (SMR, 0.47 [95% CI, 0.14-1.51]).[17]

DISCUSSION

The reviewed studies suggest that the risk of all-cause and cause-specific mortality is lower among NFL players than among the general population of US men.[2,3,14,16,17,19] Among NFL players, nonwhite race/ethnicity,[14,19] power positions,[14,19] and high playing-time BMI (≥30 kg/m^2)[2,19]

were associated with elevated all-cause and cardiovascular mortality risks. NFL speed position players (vs US men) had an elevated risk of neurodegenerative-related death.[16] Overall, however, a number of methodological issues associated with all-cause and cause-specific mortality risk factors among NFL players in the existing literature[6-11] preclude a definitive conclusion of etiological protective or risk effects.

One issue is that the all-cause and cause-specific SMR measure of association is prone to considerable bias because the case fatality rate and associated duration of illness vary widely between NFL players and the general population of US men. The case fatality rates of underlying causes of death such as cardiovascular disease are likely lower among NFL players than the general population of US men. Even when adjusted for potential confounders (playing-time BMI, age, race/ethnicity, and career length), the life span advantage conferred by health care access and quality (ie, early diagnosis, more effective treatment, and care that leads to better health outcomes) received by NFL players probably outweighs that of the general population. This is true even if an underlying cause of death (eg, CTE and related neurodegenerative diseases) is more prevalent among NFL players.[26] On the other hand, differences in health care between NFL players and the general population of US men may lead to the differential misclassification of underlying and contributory causes of death, resulting in an overestimate of certain causes (eg, neurodegenerative disease) among NFL players because of diagnostic suspicion. This bias is likely lower in NFL research studies conducted after the initiation of the NDI in 1979, which required rigorous fidelity checks for consistency in cause of death definitions at the state and national levels.

A second issue is that the underlying causes of death related to chronic diseases (specifically, cardiovascular disease) are set in train long before a clinical diagnosis is possible[20,32]; therefore, measuring risk factors earlier in life among NFL players may provide more relevant etiological measures of risk than relying on time-dependent risk factors during and after a player's NFL career. Indeed, the differentially long latency associated with chronic diseases may explain the differential effects of playing-time BMI observed on all-cause and cardiovascular-related mortality between reference periods examined in the existing literature.[1-3,14,16,19] Moreover, existing evidence shows that the net effects of adulthood exposures on chronic disease and mortality risk are low to moderate at best.[4,5,12] Therefore, early-life exposures examined via a life-course approach are critical to the valid identification of etiological risk factors related to early mortality among NFL players.

A third issue is that estimating SMR entails determining the number of expected deaths in a standard population (ie, standard NFL and US male population) via a statistical model and then computing the observed/expected ratio. For comparisons made in the studies that we reviewed,[1-3,14,16,17,19] what constitutes a "standard population" is clearly different between the 2 groups being compared, and therefore, the use of direct "observed" deaths likely overestimates the risk in the smaller NFL population. To the extent that football can differentially influence health and

hence mortality between NFL players and US men, SMR comparisons are a useful measure of association; however, they may overestimate the attributable risk or "cause-specific mortality."

All-cause and cardiovascular mortality risk differences by player position and playing-time BMI for within-NFL cohort comparisons provide some insights into the comparability issue of "healthy worker effect." Specifically, our findings showed that obesity was associated with a higher risk of all-cause mortality in the general US male population than in the NFL population (irrespective of NFL career length). This suggests that at a comparable BMI, a person in the general population is at a higher risk of mortality than an NFL player is. Here, the "healthy worker effect" bias is a function of the fact that only healthy and physically fit men self-select or choose to draft for the NFL; moreover, healthier players are less likely to have short NFL careers. The impact of this bias is exacerbated in the studies by Baron et al,[3] Lehman et al,[16] and Lincoln et al[19] in which player inclusion is based on the number of seasons played. To address this issue, future studies should consider the use of dynamic cohort designs (including the collection of time-varying variables or risk factors) in which players enter the study sample when drafted into the NFL and are evaluated after their NFL careers. This should be augmented with pre-NFL exposure information (eg, high school and college participation in football) for a more complete view of relevant football-related etiological risk factors. Consideration of these critical exposure windows will ensure a valid inference about suspected etiological risk factors.

The health benefits associated with higher levels of physical activity and fitness among NFL players versus the general population of US men are irrefutable.[18] However, there are mixed findings for the relationships between training loads, injury risk, fitness, and performance in athlete populations.[13] Studies among rugby players suggest that training and competition stress result in muscle damage,[34] reduced neuromuscular function,[23] impaired immune systems,[10] and anabolic-catabolic homeostasis.[25] Given the similarities in physical activity requirements between rugby and football, these findings lend credence to the hypothesis of premature or accelerated aging due to traumatic body injuries. On the other hand, it is plausible that the injury risk is not increased by training per se but rather excessive and rapid increases in training loads in contact sports.[11] These relationships warrant further examination in football populations in which severe injuries such as concussions and resulting CTE are prevalent.[26]

With more valid "control" comparisons (eg, other professional sport players), an elevated underlying and contributory cause-specific (eg, neurodegenerative, cerebrovascular, or musculoskeletal diseases) mortality risk among NFL players is not improbable. A recent examination of repeated head impacts through tackle football before the age of 12 years in 42 players demonstrated that children and adolescents are susceptible to prolonged later-life neurological impairment.[33] These negative effects remain, even after adjusting for differences in NFL career length and highest level of education attained. In fact, despite having shorter

NFL careers, players exposed to body and brain trauma at younger ages (<12 years) had significantly lower executive function.[33] NFL exposure probably accelerates the pathophysiological mechanisms toward neurological deficits (observed among NFL players with short careers) as a result of the accumulation of traumatic injury incidents.[8]

These early-life exposures may also be correlated with other causes of death such as suicide. This is supported by findings of an elevated suicide risk among National Collegiate Athletic Association (NCAA) football players compared with age- and race/ethnicity-matched male athletes.[30] Rao et al[30] showed that the risk of suicide (linked to mental health problems) was more than 2-fold (relative risk, 2.21 [95% CI, 1.05-4.61]) higher among football players than other athletes. Demonstrably, this finding underlines questions about the validity of evidence based on comparing the mortality risk among NFL players to that of the general population of US men. However, alternative explanations related to the differences between NFL and NCAA football players (eg, age of players and how they respond to stress) should not be ignored.

Additionally, potential confounding by the higher prevalence of known chronic disease risk factors such as tobacco smoking[29] and family history[7,31] in the general population of US men (vs NFL player population) likely functions to underestimate (bias) the mortality risk among NFL players. Future studies need to control for these confounders. NFL reference period/season-related factors, particularly those linked to body and head trauma (eg, number of games played, number of concussions), and their relation to neurodegenerative disease mortality also require more research.

CONCLUSION

This systematic review represents a comprehensive epidemiological evaluation of the etiological risk factors associated with early mortality among NFL players. Overall, the mortality risk among NFL players appeared to be lower than that in the general population of US men. However, methodological issues associated with all-cause and cause-specific mortality risk factors examined in the existing literature preclude a definitive conclusion of etiological protective or risk effects. Comparison groups less prone to selection bias ("healthy worker effect") and a life-course evaluation of suspected risk factors are warranted.

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APPENDIX

TABLE A1
Measures of Association Between Overall Mortality and Selected Risk Factors
Among Current and Previous NFL Players[a]

Risk Factor	Measure of Association	Comparison Group	Summary
NFL player			
Baron et al[3] (2012)	SMR, 0.53 (95% CI, 0.48-0.59)	US men	NFL players in the 1959-1988 seasons had decreased
Lincoln et al[19] (2018)	SMR, 0.46 (95% CI, 0.40-0.52)	US men	overall mortality compared to US men (Baron and
Abel and Kruger[1] (2006)	Longer mean life expectancy[b]: 6.1 ± 11.9 y	US men	Rinsky[2]; Abel and Kruger[1]). The risk was 7% lower in an updated analysis (Lincoln et al[19]), reflecting
Lehman et al[17] (2016)	≥5 seasons: SMR, 0.60 (95% CI, 0.55-0.65)	US men	the potential impact of stricter and safer rule changes. The risk was also 12% lower among
Baron and Rinsky[2] (1994)	≥5 seasons[c]: SMR, 0.54 (95% CI, 0.44-0.66)	US men	players with <5 credited seasons (Baron and Rinsky[2]), suggesting that a lower risk is associated
	<5 seasons[c]: SMR, 0.42 (95% CI, 0.30-0.59)		with shorter playing exposure.
Koning et al[14] (2014)	Not reported	US men	
Venkataramani et al[36] (2018)	Career NFL player[d]: HR, 1.38 (95% CI, 0.95-1.99)	NFL replacement players	
Race/ethnicity			
Baron and Rinsky[2] (1994)	White with ≥5 seasons: SMR, 0.63 (95% CI, 0.49-0.79)	US men	There was a slightly stronger protective effect among nonwhite than white players irrespective of playing
	White with <5 seasons: SMR, 0.47 (95% CI, 0.51-1.97)		duration among players during 1959-1988. An updated analysis including 1959-1994 and 1959-
	Nonwhite with ≥5 seasons: SMR, 0.43 (95% CI, 0.30-0.60)	US men	2012 showed a reverse effect: a higher risk among nonwhite players (Lincoln et al[19]) and no
	Nonwhite with <5 seasons: SMR, 0.40 (95% CI, 0.24-0.60)		association in 1994 (Koning et al[14]).
Lincoln et al[19] (2018)	White: SMR,[e] 0.39 (95% CI, 0.30-0.50)	US men	
	Nonwhite: SMR,[e] 0.48 (95% CI, 0.41-0.56)		
	Nonwhite: SMR,[e] 1.63 (95% CI, 1.21-2.21)	White players	
Koning et al[14] (2014)	1970: white: HR, 0.67 (*P* = .02)	Nonwhite players	
	1994: white: HR, 1.03 (*P* = .93)		

(continued)

TABLE A1 (continued)

Risk Factor	Measure of Association	Comparison Group	Summary
Position			
Abel and Kruger[1] (2006)	ANCOVA (P > .05)	NFL/US men	Using an older NFL cohort (1940-2004), Abel and Kruger[1] found no association between player position and longevity. The differential protective effect by position shown by Lincoln et al[19] was likely caused by rule changes. The differing risks for injury were underscored by a higher mortality risk among power and specialist versus speed players.
Lincoln et al[19] (2018)	Speed: SMR, 0.36 (95% CI, 0.30-0.44)	US men	
	Power: SMR, 0.72 (95% CI, 0.59-0.87)		
	Specialist: SMR, 0.22 (95% CI, 0.09-0.43)		
	Power: SMR, 2.16 (95% CI, 1.62-2.86)	Speed positions	
	Specialist: SMR, 1.25 (95% CI, 0.36-4.33)		
Koning et al[14] (2014)	1970: skill-based player[f]: HR, 0.62 (P < .01)	Lineman positions[g]	
	1994: skill-based player: HR, 0.19 (P = .01)		
	1970: other: HR, 0.54 (P = .01)		
	1994: other: HR, 0.71 (P = .30)		
Career years			
Abel and Kruger[1] (2006)	ANCOVA (P < .01)	NFL/US men	There was a linear increase in longevity with a longer playing career irrespective of NFL cohort period (compared with US men). No difference was found within NFL players based on career length (Lincoln et al[19]), while Koning et al[14] showed that the risk increased with more games played in the 1970 season.
Lehman et al[17] (2016)	≥5 seasons: SMR, 0.60 (95% CI, 0.55-0.65)	US men	
Baron and Rinsky[2] (1994)	≥5 seasons[c]: SMR, 0.54 (95% CI, 0.44-0.66)	US men	
	<5 seasons[c]: SMR, 0.42 (95% CI, 0.30-0.59)		
Lincoln et al[19] (2018)	1-4 years: SMR, 0.47 (95% CI, 0.39-0.57)	US men	
	≥5 years: SMR, 0.44 (95% CI, 0.37-0.53)		
	≥5 years: SMR, 0.96 (95% CI, 0.70-1.31)	1-4 years/NFL	
Koning et al[14] (2014)	1970: long career of ≥27 games: HR, 4.47 (P = .01)	≤2 games	
	1994: long career of ≥27 games: HR, 0.74 (P = .60)		
BMI			
Abel and Kruger[1] (2006)	ANCOVA (r^2 = 0.01, P < .01)	NFL/US men	The mortality risk increased with a higher BMI for both internal and external group comparisons.
Lincoln et al[19] (2018)	<30 kg/m²: SMR, 0.31 (95% CI, 0.25-0.39)	US men	
	30-34 kg/m²: SMR, 0.46 (95% CI, 0.36-0.58)		
	≥35 kg/m²: SMR, 1.12 (95% CI, 0.87-1.44)		
	30-34 kg/m²: SMR, 1.51 (95% CI, 1.10-2.06)	BMI <30 kg/m²/NFL	
	≥35 kg/m²: SMR: 3.84 (95% CI, 2.66-5.54)		

[a]ANCOVA, analysis of covariance; BMI, body mass index; HR, hazard ratio; NFL, National Football League; SMR, standardized mortality ratio; US, United States.

[b]Model adjusted for age, BMI, and player position.

[c]Model adjusted for age and race.

[d]Model adjusted for birth year, BMI, height, and player position.

[e]Model adjusted for age and calendar year.

[f]Skill-based players: wide receivers, tight ends, quarterbacks, and running backs.

[g]Lineman positions: offensive and defensive linemen.

TABLE A2
Measures of Association Between Cardiovascular Mortality
and Selected Risk Factors Among Current and Previous NFL Players[a]

Risk Factor	Measure of Association	Comparison Group	Summary
NFL player			
Baron et al[3] (2012)	SMR, 0.68 (95% CI, 0.56-0.81)	US men	NFL players in the 1959-1988 seasons
Lehman et al[16] (2012)	SMR, 0.71 (95% CI, 0.64-0.79)	US men	had decreased overall mortality
Lincoln et al[19] (2018)	SMR, 0.68 (95% CI, 0.50-0.90)	US men	compared to US men.
Position			
Baron et al[3] (2012)	Category I player[b]: SMR, 0.48 (95% CI, 0.33-0.67)	US men	Compared to US men, all NFL players
	Category II player[c]: SMR, 0.52 (95% CI, 0.35-0.74)	US men	had a lower risk of cardiovascular mortality. Within-NFL comparisons
	Category II player[d]: HR, 1.01 (95% CI, 0.57-1.78)	Category I players	showed that defensive linemen had a
	Defensive lineman[d]: HR, 1.86 (95% CI, 0.96-3.62)	Category I players	higher risk than other positions even
	Offensive lineman[d]: HR, 0.90 (95% CI, 0.43-1.86)	Category I players	with adjustment for BMI, age,
	Defensive lineman: SMR, 1.42 (95% CI, 1.02-1.92)	US men	calendar year, and race/ethnicity. The power position–cardiovascular
	Offensive lineman: SMR, 0.70 (95% CI, 0.45-1.05)	US men	mortality relationship is probably
Baron and Rinsky[2] (1994)	Lineman with ≥5 seasons: SMR, 1.15 ($P > .05$)	US men	confounded by BMI (Lincoln et al[19]).
	White lineman with ≥5 seasons: SMR, 1.18 ($P > .05$)	US men	
	Nonwhite lineman with ≥5 seasons: SMR, 1.05 ($P > .05$)	US men	
	Running back, tight end, and linebacker with ≥5 seasons: SMR, 0.43 ($P > .05$)	US men	
	White running back, tight end, and linebacker with ≥5 seasons: SMR, 0.35 ($P > .05$)	US men	
	Nonwhite running back, tight end, and linebacker with ≥5 seasons: SMR, 0.56 ($P > .05$)	US men	
	Quarterback, receiver, defensive back, kicker, and special teams: SMR, 0.43 ($P > .05$)	US men	
	White quarterback, receiver, defensive back, kicker, and special teams: SMR, 0.43 ($P > .05$)	US men	
	Nonwhite quarterback, receiver, defensive back, kicker, and special teams: SMR, 0.29 ($P > .05$)	US men	
	Running back, linebacker, and tight end[e]: OR, 1.05 (95% CI, 0.34-3.18)	Other positions	
	Offensive/defensive lineman[e]: OR, 3.70 (95% CI, 1.51-9.07)	Other positions	
Lincoln et al[19] (2018)	Power: SRR, 2.99 (95% CI, 1.67-5.37)	Speed positions	
	Specialist: SRR, 2.12 (95% CI, 0.28-15.87)		
BMI			
Baron et al[3] (2012)	25-<30 kg/m²[d]: HR, 0.80 (95% CI, 0.39-1.65)	BMI 18.5-<25 kg/m²	There was a consistent elevated BMI association with the cardiovascular
	≥30 kg/m²[d]: HR, 1.58 (95% CI, 0.66-3.78)		risk compared to other NFL players
Baron and Rinsky[2] (1994)	28-31 kg/m²[f]: OR, 2.58 (95% CI, 0.95-6.99)	BMI <28 kg/m²	and US men even with adjustment
	≥32 kg/m²[f]: OR, 6.04 (95% CI, 2.18-7.08)		for age, calendar year, and race/
Lincoln et al[19] (2018)	30-34.9 kg/m²: SRR, 3.90 (95% CI, 1.54-5.87)	BMI <30 kg/m²	ethnicity. The potential effect
	≥35 kg/m²: SRR, 9.03 (95% CI, 4.20-19.41)		modification by position and calendar year needs further research.
Race/ethnicity			
Baron et al[3] (2012)	Nonwhite[d]: HR, 1.57 (95% CI, 1.15-2.55)	White players	There was a higher risk among
Baron and Rinsky[2] (1994)	Nonwhite[e]: OR, 1.70 (95% CI, 1.01-2.98)	White players	nonwhite players adjusted for
	Nonwhite[f]: OR, 1.70 (95% CI, 1.01-2.95)	White players	position, reference period, and BMI.
	White with ≥5 seasons: SMR, 0.83 (95% CI, 0.53-1.25)	US men	The potential influence of postcareer effects was unexamined.
	Nonwhite with ≥5 seasons: SMR, 0.95 (95% CI, 0.47-1.79)	US men	
	White with <5 seasons: SMR, 0.44 (95% CI, 0.01-2.45)	US men	

(continued)

TABLE A2 (continued)

Risk Factor	Measure of Association	Comparison Group	Summary
	Nonwhite with <5 seasons: SMR, 0.74 (95% CI, 0.15-2.17)	US men	
Lincoln et al[19] (2018)	Nonwhite: SRR, 3.00 (95% CI, 1.54-5.87)	White players	
Reference period			
Baron et al[3] (2012)	1980-1989[d]: HR, 0.78 (95% CI, 0.35-1.78) 1990-1999[d]: HR, 0.45 (95% CI, 0.19-1.07) 2000 and after[d]: HR, 0.28 (95% CI, 0.12-0.71)	Before 1980	The reducing risk in recent reference periods was potentially linked to injury-averse changes in NFL game rules.
Career years			
Baron and Rinsky[2] (1994)	≥5 seasons: SMR, 0.87 (95% CI, 0.60-1.22) <5 seasons: SMR, 0.63 (95% CI, 0.17-1.62)	US men	The lack of an association may be suggestive of a stronger influence of postcareer effects.
Lincoln et al[19] (2018)	≥5 seasons: SRR, 0.84 (95% CI, 0.50-1.44)	1-4 years	

[a]BMI, body mass index; HR, hazard ratio; NFL, National Football League; OR, odds ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States.
[b]Category I players: defensive back, punter/kicker, punter, quarterback, and wide receiver.
[c]Category II players: fullback, halfback, linebacker, offensive end, running back, and tight end.
[d]Model adjusted for age, BMI, race, calendar year, and playing position.
[e]Model adjusted for race and position category.
[f]Model adjusted for race and BMI.

TABLE A3
Measures of Association Between Injury-Related Mortality
and Selected Risk Factors Among Current and Previous NFL Players[a]

Risk Factor	Measure of Association	Comparison Group	Summary
NFL player (all injuries)			
Lehman et al[16] (2012)	SMR,[b] 0.63 (95% CI, 0.45-0.86) SMR,[c] 0.69 (95% CI, 0.52-0.89)	US men	There was a lower risk of injury-related death among NFL players versus US men.
Lincoln et al[19] (2018)	Transportation: SMR, 0.65 (95% CI, 0.45-0.91) All other: SMR, 0.41 (95% CI, 0.26-0.62)	US men	
Career years (CTE)			
McKee et al[23] (2013)	Spearman test ($r = 0.81$, $P < .01$)	NFL subanalysis	There was a positive association with stage of CTE at death.
Retirement years (CTE)			
McKee et al[23] (2013)	Spearman test ($r = 0.75$, $P < .01$)	NFL subanalysis	There was a positive association with stage of CTE at death.
Age at death (CTE)			
McKee et al[23] (2013)	Spearman test ($r = 0.81$, $P < .01$)	NFL subanalysis	There was a positive association with stage of CTE at death. The mean latency period for CTE symptoms was 13 years.
No. of concussions (CTE)			
McKee et al[23] (2013)	Spearman test ($r = 0.26$, $P = .18$)	NFL subanalysis	There was no association with CTE stage.
Education (CTE)			
McKee et al[23] (2013)	Spearman test ($r = 0.26$, $P = .13$)	NFL subanalysis	There was no association with CTE stage.
Lifetime steroid use (CTE)			
McKee et al[23] (2013)	Mann-Whitney test ($P = .73$)	NFL subanalysis	There was no association with CTE stage.
Position (CTE)			
McKee et al[23] (2013)	Kruskal-Wallis test ($P = .41$)	NFL subanalysis	There was no association with CTE stage.

[a]CTE, chronic traumatic encephalopathy; NFL, National Football League; SMR, standardized mortality ratio; US, United States.
[b]Underlying cause of death on death certificate.
[c]Both underlying and contributing cause of death on death certificate.

TABLE A4
Measures of Association Between Neurodegenerative Mortality
and Selected Risk Factors Among Current and Previous NFL Players[a]

Risk Factor	Measure of Association	Comparison Group	Summary
NFL player			
Lehman et al[16] (2012)	All: SMR,[b] 2.83 (95% CI, 1.36-5.21) All: SMR,[c] 3.26 (95% CI, 1.90-5.22)	US men	There was a higher risk of neurodegenerative mortality among NFL players versus US men.
	Dementia/Alzheimer: SMR,[b] 1.80 (95% CI, 0.22-6.50) Dementia/Alzheimer: SMR,[c] 3.86 (95% CI, 1.55-7.95)	US men	As both an underlying and contributing cause, the dementia/Alzheimer risk was higher among NFL players versus US men.
	ALS: SMR,[b] 4.04 (95% CI, 1.48-8.79) ALS: SMR,[c] 4.31 (95% CI, 1.73-8.87)	US men	The ALS risk was higher among NFL players than US men.
	Parkinson: SMR,[b] 2.14 (95% CI, 0.26-7.75) Parkinson: SMR,[c] 1.69 (95% CI, 0.35-4.94)	US men	There was no difference in Parkinson disease between NFL players and US men.
Position			
Lehman et al[16] (2012)	Speed[d]: all: SRR, 3.29 (95% CI, 0.92-11.70) Speed: dementia/Alzheimer: SRR, 5.96 (95% CI, 0.72-49.60) Speed: ALS: SRR, 3.88 (95% CI, 0.47-3.22) Speed: Parkinson: SRR, 1.19 (95% CI, 0.11-13.20)	Nonspeed positions[e]	There were no differences in the risk of neurodegenerative disease by player position.

[a]ALS, amyotrophic lateral sclerosis; NFL, National Football League; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States.
[b]Underlying cause of death on death certificate.
[c]Both underlying and contributing cause of death on death certificate.
[d]Speed positions: quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker (excluded: punters and kickers).
[e]Nonspeed positions: defensive and offensive linemen (excluded: punters and kickers).

TABLE A5
Measures of Association Between Violence/Suicide Mortality
and Selected Risk Factors Among Current and Previous NFL Players[a]

Risk Factor	Measure of Association	Comparison Group	Summary
Violence			
NFL player			
Lehman et al[16] (2012)	SMR, 0.27 (95% CI, 0.14-0.46)	US men	Violence-related deaths were lower among NFL players versus US men.
Lincoln et al[19] (2018)	SMR, 0.38 (95% CI, 0.27-0.52)	US men	
Suicide			
NFL player			
Lehman et al[17] (2016)	≥5 seasons: SMR, 0.47 (95% CI, 0.24-0.82)	US men	Both violence/suicide-related deaths were lower among NFL players versus US men.
Position			
Lehman et al[17] (2016)	Nonspeed[b] with ≥5 seasons: SMR, 0.65 (95% CI, 0.24-1.42) Speed[c] with ≥5 seasons: SMR, 0.39 (95% CI, 0.14-0.86)	US men	Compared with US men, the risk of suicide was lower among NFL players irrespective of the position played. The position played was not associated with suicide among NFL players.
	Speed with ≥5 seasons: SMR, 0.47 (95% CI, 0.14-1.51)	Nonspeed positions	

[a]NFL, National Football League; SMR, standardized mortality ratio; US, United States.
[b]Nonspeed positions: defensive and offensive linemen (excluded: punters and kickers).
[c]Speed positions: quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker (excluded: punters and kickers).