

Exposure to American Football and Neuropsychiatric Health in Former National Football League Players

Findings From the Football Players Health Study

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Background: Former American football players have a higher prevalence of cognitive impairment than that of the US general population. It remains unknown what aspects of playing football are associated with neuropsychiatric outcomes.

Hypothesis: It was hypothesized that seasons of professional football, playing position, and experience of concussions were associated with cognition-related quality of life (QOL) and indicators of depression and anxiety.

Study Design: Descriptive epidemiology study.

Methods: The authors examined whether seasons of professional football, playing position, and experience of concussions, as measured by self-report of 10 symptoms, were associated with cognition-related QOL and indicators of depression and anxiety in a cross-sectional survey conducted 2015 to 2017. Cognition-related QOL was measured by the short form of the Quality of Life in Neurological Disorders: Applied Cognition–General Concerns. The Patient Health Questionnaire–4 measured depression and anxiety symptoms. Of 13,720 eligible men with apparently valid contact information, 3506 players returned a questionnaire at the time of this analysis (response rate = 25.6%).

Results: Seasons of professional play (risk ratio [RR] per 5 seasons = 1.19, 95% CI = 1.06–1.34) and playing position were associated with cognition-related QOL. Each 5 seasons of play was associated with 9% increased risk of indicators of depression at borderline statistical significance ($P = .05$). When compared with former kickers, punters, and quarterbacks, men who played any other position had a higher risk of poor cognition-related QOL, depression, and anxiety. Concussion symptoms were strongly associated with poor cognition-related QOL (highest concussion quartile, RR = 22.3, $P < .001$), depression (highest quartile, RR = 6.0, $P < .0001$), and anxiety (highest quartile, RR = 6.4, $P < .0001$), even 20 years after last professional play.

Conclusion: The data suggest that seasons of play and playing position in the NFL are associated with lasting neuropsychiatric health deficits. Additionally, poor cognition-related QOL, depression, and anxiety appear to be associated with concussion in the long term.

Keywords: sports injuries; postconcussion syndrome; cognitive function; depression; anxiety; football

Cognitive impairment,^{9,13} depression,^{12,14,30,31} and anxiety^{29,31,34} are established acute sequelae of concussion. Recently, public attention has focused on the long-term health of former professional American-style football players as an occupational group exposed to an unusually high number of concussions and subconcussive blows. Several

studies have compared the prevalence of neurological disorders and cognitive function between former National Football League (NFL) players and the general population, finding prevalence rates of neurodegenerative disease mortality³³ and cognitive impairment far higher than expected in NFL players.^{16,41,51} Smaller studies with convenience samples found deficits in neuropsychiatric function and brain abnormalities as well as chronic traumatic encephalopathy in the postmortem brains of former players.^{2,20,35} Although studies have found a similar prevalence of major depression in NFL players versus the general public,^{43,51}



whether depression or anxiety is associated with seasons of NFL play or playing position is unknown. More generally, the extent to which depression and anxiety may be long-term sequelae of concussion is also largely unknown,^{17,24,26} as concussion studies have predominantly had <1 year of follow-up.[†]

Current findings suggest that playing in the NFL may cause increased risk of cognitive problems and neurodegenerative disease^{2,16,33,35,41,51}; however, existing studies had several important limitations. Most studies did not account for factors that differ between NFL players and the general population. NFL players typically participated extensively in youth and college sports, which carry risk of concussion and subconcussive blows.[‡] These exposures before NFL play may account for some of the neuropsychiatric risk in former NFL players versus the general population.^{1,47-50} For example, 2 of 3 samples that included former NFL players reported that playing organized football before age 12 years was associated with cognitive deficits and depression.^{1,47-50} Postmortem brain studies provided evidence that former players with neuropsychiatric symptoms had physical abnormalities in brain structure. However, these studies suffered from potential selection bias in that they were overwhelmingly composed of men who had neuropsychiatric symptoms in life. Thus, the magnitude of risk and specific factors of NFL play associated with subsequent cognitive and mood problems remains unknown. Studies comparing former NFL players with one another in a sample not selected for neuropsychiatric symptoms could mitigate some of these methodological issues. A dose-response association of neuropsychiatric outcomes with seasons of NFL play would provide evidence for the hypothesis that professional football causes worse neuropsychiatric outcomes.^{13,23} A lack of such an association would be evidence against causation.

Studies of former NFL players have examined the association of self-reported concussions and cognitive impairment,¹⁶ physician's diagnosis of Alzheimer disease,¹⁶ and depression,^{17,40} with varied findings. However, although a longitudinal validation study found that self-reported concussions had moderate reliability, their use as an exposure measure may be

problematic. Players whose physical and mental health declined between surveys tended to report more concussions in the second survey as compared with the first, suggesting that current health influenced report of past concussions.²⁷ Additionally, medical records of concussions have poor agreement with athlete recollections, owing to nondisclosure or non-treatment.²⁸ Thus, seasons of play and playing position, which are associated with concussions,^{9,38} may serve as less biased, more reliably recalled exposure measures than direct reporting of concussion exposure.

In the present study, we examined whether seasons of play and playing position in the NFL were associated with poor cognition-related quality of life (QOL), depression, and anxiety in a large sample of former players: the Football Players Health Study (FPHS). We further examined whether self-reported concussion symptoms during playing years explained possible associations. As nonhead injury and pain have been associated with cognitive function, depression, and anxiety,^{4,19,45} we examined associations of our exposures further adjusted for these factors. We accounted for age at which organized football was first played in these analyses, and we examined the independent association of age at first football with the outcomes.

METHODS

Sample

Our study targeted former players who participated in the NFL since 1960, the year the transition to helmets with hard plastic shells was essentially complete. We obtained home or email addresses from the NFL Players Association for 14,906 players, of which 1186 were returned as invalid. The remaining 13,720 players were mailed or emailed a questionnaire. At the time of this analysis, 3506 players had responded. The study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

Measures

Football Exposures. Players were asked to indicate the positions that they most often played professionally.

[†]References 6, 7, 12, 14, 15, 25, 29-31, 34, 46, 52.

[‡]References 1, 5, 12, 18, 26, 36, 42, 49, 50.

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Response options included offensive line, defensive line, linebacker, defensive back, running back, wide receiver, tight end, quarterback, kicker/punter, and special teams. The reference category was kicker/punter. As nearly every player who played special teams also listed an offensive or defensive position, we created an additional variable to indicate participation in special teams, in 3 levels: none; “special strength” for players who also played offensive or defensive line or tight end; and “special speed” for players who also played running back, wide receiver, defensive back, or linebacker. For 10 men who did not select a position, we identified their NFL playing position via internet search.

Players were asked, “How many seasons did you actively practice or play professional football?” Additionally, the first and last calendar years of professional play were queried. Seventy-five men were missing seasons of play. We obtained data for 53 men from Pro Football Reference.³⁷ The remaining 22 men were excluded in analyses with this variable.

We queried 10 football-related concussion symptoms during playing years with the following: “While playing or practicing football, did you experience a blow to the head, neck, or upper body followed by: headaches, nausea, dizziness, loss of consciousness, memory problems, disorientation, confusion, seizure, visual problems, and feeling unsteady on your feet?” Response options for each symptom were as follows: no, once, 2-5, 6-10, or 11+ times. We coded these as 0, 1, 3.5, 8, and 13 and calculated the mean across all 10 items. We divided this mean by seasons of professional play to create a mean concussion symptom score per season. Last, we calculated quartiles of the concussion score to examine a possible dose-response between symptoms and neuropsychiatric outcomes. We additionally created 3 groups of playing positions based on mean concussion symptoms at the time of head impact per season averaged across all players in that position: (1) low—kickers, punters, and quarterbacks; (2) medium—wide receivers, defensive backs, linemen, tight ends; and (3) high—running backs, linebackers, and special teams.

Players were asked, “How old were you when you began to play organized football?” We dichotomized age at first play as <12 or ≥12 years based on prior research.^{1,49} A small number of men (n = 47) were missing age at first play and were excluded in analyses with this variable.

Cognition-Related QOL. The short form of the Quality of Life in Neurological Disorders: Applied Cognition—General Concerns (Neuro-QOL) was used to assess cognition-related QOL.¹⁰ Eight items queried past 7-day cognitive difficulties (eg, “I had to read something several times to understand it”). Response options were as follows: 0, never; 1, rarely (once); 2, sometimes (2-3 times); 3, often (once/day); or 4, very often (several times/day). Responses were summed to create a continuous measure. A US population sample (N = 1109) was used to create standardized T scores with a mean of 50 and an SD of 10.¹⁰ On the basis of published guidelines, we created an indicator of “severe symptoms or impairment” using a score ≤30, which corresponds to ≤2 SD below the US population mean (approximately equivalent to the lowest 2.5% of the US population).²¹

The short form had excellent internal consistency in our data (Cronbach alpha = .97). Ten men did not respond to the Neuro-QOL questions and were excluded in these analyses.

Indicators of Depression and Anxiety. The Patient Health Questionnaire-4 (PHQ-4) assessed symptoms of depression and anxiety. The PHQ-4 queries 2 depression symptoms in the past 2 weeks (the PHQ-2: “Little interest or pleasure in doing things” and “Feeling down, depressed or hopeless”) and 2 anxiety symptoms (the Generalized Anxiety Disorder Scale-2: “Feeling nervous, anxious or on edge” and “Not being able to stop or control worrying”). Response options included the following: 0, not at all; 1, several days; 2, more than half the days; 3, nearly every day. Responses were summed separately for depression and anxiety and dichotomized at ≥3 for each, indicating high depressive symptoms or high anxiety symptoms. In a meta-analysis of 4 studies, a cutoff of 3 had a sensitivity of 0.76 and a specificity of 0.81.^{32,39} Current use of medication for depression and anxiety was queried separately (each coded yes/no). Men were considered to have indicators of depression if they met the PHQ-2 cutoff or were taking medications for depression. Men were considered to have indicators of anxiety if they met the Generalized Anxiety Disorder Scale-2 cutoff or were taking medications for anxiety. Three men did not respond to the PHQ-4 and were excluded.

Pain Medication and Surgery. Pain medication use was queried with the following: “During your active playing years, did you take pain control medications once a week or more (not just for an acute injury)?” Response options included aspirin or Tylenol, ibuprofen, and prescription medication use. As only prescription pain medication use was associated with our outcomes, we included only that variable in subsequent models. Experience of 7 types of surgery during playing years was queried: anterior cruciate ligament reconstruction, neck, back, knee, ankle, shoulder, and hand surgery. We created a count of the number of types of surgery from these responses (eg, a player who had at least 1 neck, hand, and back surgical procedure would have had 3 types of surgical procedures).

Demographic Factors. Race was coded as black, white, or other. Age at questionnaire was in years.

Statistical Analyses

To investigate potential participation bias, we compared FPHS responders with nonresponders. Nonresponders were men whom we attempted to contact who did not join the study. Data for 7772 nonresponders were obtained through linkage with the Pro Football Reference data set (which includes only players with regular- or postseason statistics).³⁷ We also compared the racial distribution of the FPHS with that of a prior stratified random sample of pension-eligible NFL retirees.⁵¹

We ascertained the prevalence of poor cognition-related QOL, depression, and anxiety by player position and number of professional seasons. Next, to determine the association of our outcomes with position and professional

TABLE 1
NFL Player Characteristics: Football Players Health Study (n = 3506)^a

	n	Age, y	Professional Seasons, n	Age at First Organized Football, y	Concussion Symptoms, n	Loss of Consciousness, n	Race: White
Total	3506	52.8 ± 14.2	6.8 ± 3.7	11.8 ± 3.1	3.2 ± 2.8	1.6 ± 2.6	58.6 (2053)
Seasons in the NFL							
1	137	48.9 ± 13.9	1.0 ± 0.1	11.3 ± 3.2	2.5 ± 2.4	1.2 ± 2.3	69.3 (95)
2-4	977	49.6 ± 14.4	3.1 ± 0.8	11.5 ± 3.2	2.9 ± 2.6	1.4 ± 2.3	59.4 (580)
5-6	707	52.3 ± 14.7	5.4 ± 0.5	11.7 ± 3.1	3.1 ± 2.7	1.6 ± 2.5	55.9 (395)
7-9	817	54.7 ± 13.8	7.9 ± 0.8	11.8 ± 3.0	3.4 ± 2.8	1.8 ± 2.8	56.2 (459)
≥10	846	55.9 ± 12.8	12.0 ± 2.1	12.2 ± 3.1	3.4 ± 3.0	1.9 ± 2.7	60.9 (515)
Position							
Kicker/punter	107	51.9 ± 12.5	8.8 ± 5.4	13.7 ± 3.7	1.3 ± 1.7	0.6 ± 1.1	91.6 (98)
Quarterback	152	55.2 ± 13.3	9.0 ± 4.7	11.4 ± 3.0	2.0 ± 1.6	1.3 ± 1.5	91.4 (139)
Wide receiver	331	51.6 ± 14.3	6.5 ± 3.7	11.5 ± 3.2	2.7 ± 2.5	1.8 ± 2.5	42.6 (141)
Tight end	255	50.7 ± 14.9	6.7 ± 3.6	11.7 ± 3.0	3.1 ± 2.6	1.6 ± 2.6	71.8 (183)
Running back	379	55.4 ± 13.9	5.8 ± 3.1	11.5 ± 3.0	3.5 ± 2.9	1.8 ± 2.7	38.0 (144)
Offensive line	749	51.7 ± 14.3	7.0 ± 3.9	12.1 ± 2.9	3.2 ± 2.7	1.2 ± 2.3	80.9 (606)
Linebacker	571	52.7 ± 13.8	6.5 ± 3.4	11.4 ± 3.0	3.7 ± 3.0	2.0 ± 2.9	59.5 (340)
Defensive back	526	53.2 ± 14.3	6.4 ± 3.2	11.2 ± 3.1	3.1 ± 2.7	2.0 ± 2.8	31.9 (168)
Defensive line	436	53.6 ± 14.4	6.9 ± 3.6	12.5 ± 3.2	3.4 ± 3.1	1.6 ± 2.8	53.7 (234)
Special teams							
Did not play often	2598	52.5 ± 14.1	7.0 ± 3.9	11.9 ± 3.2	3.1 ± 2.8	1.5 ± 2.5	60.5 (1572)
Strength	216	54.6 ± 14.7	6.5 ± 3.7	12.0 ± 2.7	3.5 ± 2.8	1.9 ± 3.1	74.1 (160)
Speed	692	53.3 ± 14.2	6.2 ± 3.1	11.3 ± 3.0	3.4 ± 2.7	2.0 ± 2.7	46.4 (321)

^aValues are presented as mean ± SD or % (n). NFL, National Football League.

seasons, we fit 2 models for each outcome: (1) position, seasons of professional play, age at questionnaire, and race and (2) further adjusted for concussion symptoms at the time of head impact. Additionally, as nonhead injury and experience of pain have been associated with cognitive function, depression, and anxiety,^{3,19,45} we fit a third model further adjusted for number of surgical procedures, as an indicator of nonhead injury, and regular use of prescription pain medication during playing years. We also examined our outcomes in association with the 3 groups of playing positions.

As associations with seasons of play and position may differ by era of play, we divided players into 2 groups by the median first calendar year of play (1984) and tested for the following interaction terms: (1) seasons of play × era and (2) position × era. We conducted sensitivity analyses further adjusted for age at first organized football and, to examine the influence of outliers, with seasons of play top-coded at the 95th percentile such that >12 seasons were coded as 12 seasons.

We examined age at first organized football dichotomized at age 12 years and as a continuous variable. We fit a model for each of these exposures for cognition-related QOL, depression, and anxiety as the dependent variables adjusted for age at interview and race. Finally, as loss of consciousness may be more accurately recalled than other concussion symptoms and characterizes severe concussions,³ we conducted analyses with loss of consciousness as the exposure in association with our 3 outcomes, adjusted for age and race.

We conducted sensitivity analyses using inverse probability weighting⁴⁴ to explore possible effects of bias in study participation. We estimated probability of participation based on

position, start year, end year, and seasons of play using Pro Football Reference data for nonresponders. We fit models with participants weighted by the inverse of this probability. Statistical analyses were conducted in SAS (SAS v. 9.4, SAS Institute). We estimated risk ratios (RRs) using generalized estimating equations (PROC GENMOD).⁵³

RESULTS

Respondents had a mean age of 52.8 years (SD = 14.2) and had last played professional football <1 to 55 years before the questionnaire (median = 24 years, interquartile range [IQR] = 10-35 years) (Table 1). In comparisons of responders and nonresponders with the Pro Football Reference data set, responders played slightly more seasons of football than nonresponders (responders: median, 6, IQR, 3-9; nonresponders: median, 5, IQR, 2-8) and began their professional career earlier (responders: median, 1984, IQR, 1973-1997; nonresponders: median, 1990, IQR, 1981-1999). The distribution of positions in the FPHS differed from that of nonresponders, with offensive linemen composing a larger percentage of our sample (FPHS: 20.9% vs nonresponders: 14.8%) and defensive backs representing a smaller percentage of our sample (14.7% vs 19.0%, $P < .001$) (Table 2). The racial distribution of the FPHS was similar to that of a prior stratified random sample of pension-eligible NFL retirees (FPHS: 59% white, 38% black, 4% other races; random sample, weighted: 57% white, 41% black, 2% other races).⁵¹

One in 8 respondents reported poor cognition-related QOL (12.4%) with T scores ≤30, indicating severe

TABLE 2
Distribution of Playing Positions in the Football Players Health Study and Among Nonresponders^a

Position ^b	Football Players Health Study (n = 3506)		Nonresponders (n = 7772)	
	n	%	n	%
Kicker	192	4.9	220	2.8
Quarterback	169	4.4	304	3.9
Wide receiver	375	9.7	1009	13.0
Tight end	291	7.5	478	6.2
Running back	379	9.8	970	12.5
Linebacker	581	15.0	1063	13.7
Defensive back	573	14.7	1479	19.0
Defensive line	504	13.0	1098	14.1
Offensive line	812	20.9	1151	14.8

^aData for nonresponders were obtained through linkage with the Sports Reference Pro Football database.⁴⁸ Sample sizes per position sum to more than the total in the Football Players Health Study because players were permitted to endorse >1 position. For nonresponders, each player was assigned only 1 position.

^bChi-square, *P* < .001.

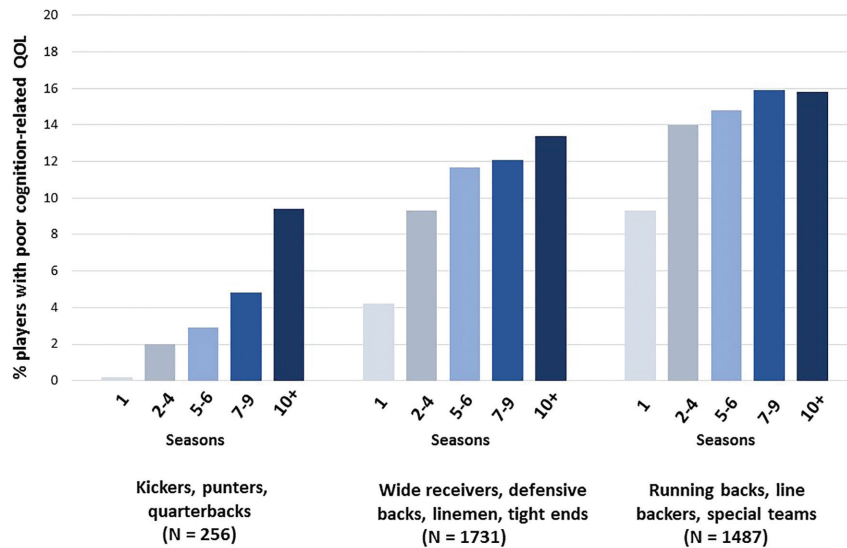


Figure 1. Poor cognition-related quality of life (QOL) by number of professional seasons and playing position among former National Football League players: Football Players Health Study (n = 3474). Poor cognition-related QOL was defined as a Neuro-QOL score ≤ 2 SD below the US population mean (*T* score ≤ 30). Positions were grouped according to the mean concussion symptoms per season for each position across all players in that position: low (≤ 2 symptoms/season: kickers, punters, and quarterbacks), medium (> 2 to 3.3 symptoms/season: wide receivers, defensive backs, linemen, tight ends), and high (> 3.3 symptoms/season: running backs, linebackers, special teams). Neuro-QOL, Quality of Life in Neurological Disorders: Applied Cognition–General Concerns.

impairment. Prevalence of poor cognition-related QOL was similar among players <55 years old (severe impairment, 13.3%; n = 248 of 1861). Cognition-related QOL was associated with seasons of professional play and playing position (Figure 1). Of men who played only 1 season, 5.8% had poor cognition-related QOL versus 12.6% of men with >1 season (*P* < .05).

Seasons of professional play (RR per 5 seasons, 1.19; 95% CI, 1.06-1.34; *P* < .01) and playing position were associated with cognition-related QOL in models adjusted for age and race (Table 3, model 1). Running backs, defensive linemen,

and linebackers were at elevated risk of poor cognition-related QOL as compared with kickers/punters.

Approximately one-quarter of respondents reported indicators of anxiety (25.9%) and depression (23.9%), and 18.3% of men reported both. Each 5 seasons of professional play was associated with a 9% increased risk of having indicators of depression, at borderline statistical significance (RR, 1.09; 95% CI, 1.00-1.18; *P* = .05) (Table 4, model 1a). Depression and anxiety were associated with playing position, with running backs and defensive linemen at higher risk as compared with kickers/punters. Risk of

TABLE 3
Risk of Poor Cognition-Related Quality of Life in Association
With Number of Professional Seasons and Playing Position: Football Players Health Study (n = 3474)^a

	n	Poor Cognition-Related Quality of Life, Risk Ratio (95% CI)		
		Model 1 ^b	Model 2 ^c	Model 3 ^d
NFL seasons (per 5 seasons)		1.19 (1.06, 1.34) ^e	1.00 (0.89, 1.13)	0.97 (0.86, 1.10)
Position				
Kicker/punter	107	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Quarterback	151	1.42 (0.50-4.00)	0.95 (0.35-2.63)	0.99 (0.36-2.71)
Wide receiver	328	2.06 (0.82-5.14)	0.95 (0.39-2.36)	1.03 (0.42-2.54)
Tight end	252	1.60 (0.61-4.18)	0.71 (0.27-1.84)	0.74 (0.29-1.92)
Running back	376	3.64 (1.49-8.90) ^e	1.31 (0.54-3.19)	1.39 (0.58-3.38)
Offensive line	747	2.31 (0.96-5.56)	0.98 (0.41-2.36)	1.00 (0.42-2.28)
Linebacker	566	2.84 (1.17-6.86) ^f	1.00 (0.42-2.42)	1.06 (0.44-2.54)
Defensive back	523	1.87 (0.76-4.61)	0.79 (0.33-1.93)	0.87 (0.36-2.12)
Defensive line	434	2.71 (1.11-6.60) ^f	1.07 (0.45-2.57)	1.13 (0.46-2.67)
Special teams				
Did not play often	2583	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Strength	215	1.21 (0.82-1.79)	1.05 (0.74-1.49)	1.05 (0.76-1.49)
Speed	686	1.05 (0.84-1.33)	1.00 (0.80-1.24)	0.99 (0.80-1.24)
Concussion symptoms during playing years				
Quartile 1	832		1.0 (Reference)	1.0 (Reference)
Quartile 2	900		3.44 (1.83-6.48) ^g	3.25 (1.73-6.12) ^g
Quartile 3	873		8.04 (4.45-14.52) ^g	7.23 (4.01-13.06) ^g
Quartile 4	879		22.25 (12.54-39.48) ^g	18.89 (10.63-33.57) ^g

^aPoor cognition-related quality of life was defined as a Neuro-QOL score ≤ 2 standard deviations below the US population mean. NFL, National Football League.

^bAdjusted for age at questionnaire and race.

^cModel 1 further adjusted for concussion symptoms during playing years.

^dModel 2 further adjusted for pain medication and surgery during playing years.

^e $P < .01$.

^f $P < .05$.

^g $P < .001$.

anxiety was not associated with seasons of professional play (Table 4, model 1b).

In analyses examining groups of positions, players in positions with medium or high mean concussion symptoms were at elevated risk of poor Neuro-QOL, depression, and anxiety as compared with players in positions with low mean concussion symptoms (Table 5, model 1, a-c).

Interaction terms for era of play with seasons of play and position were not statistically significant. Results were similar in models adjusted for age at first football, continuously or dichotomized at < 12 years, and in models with seasons of play top-coded.

Concussion symptoms at the time of football head impact were very strongly associated with subsequent cognition-related QOL, depression, and anxiety. All players above the lowest 25% of concussion symptoms were at substantially higher risk of all 3 outcomes as compared with players in the lowest 25%. The highest quartile of concussion symptoms was associated with 22.3-fold greater risk of poor cognition-related QOL, 6.0-fold greater risk of depression, and 6.4-fold greater risk of anxiety (all $P < .001$). Adjustment for concussion symptoms attenuated associations of seasons of professional play and playing position with cognition-related QOL, depression, and anxiety (Table 3, model 2; Table 4, model 2, a and b). Further

adjustment for use of prescription pain medication and number of surgical procedures during playing years somewhat attenuated associations of concussion symptoms with all 3 outcomes, although associations remained very strong (Table 3, model 3; Table 4, model 3, a and b).

In models examining the 3 outcomes in association with position group, further adjustment for concussion symptoms fully attenuated all associations (Table 5, model 2, a-c).

Loss of consciousness strongly predicted each outcome; each increase in loss of consciousness was associated with a greater prevalence of poor health (Table 6, analysis 1). Men who lost consciousness even once had substantially increased risk of all 3 outcomes as compared with men who had never lost consciousness. To further explore our findings, we conducted 2 additional analyses. First, we restricted our sample to men who had last played professional football ≥ 20 years before the questionnaire (n = 1863). In this subsample, loss of consciousness remained strongly associated with cognition-related QOL, depression, and anxiety (Table 6, analysis 2). Second, to examine the effects of concussion without loss of consciousness, we restricted our sample to men who had never lost consciousness. Estimates were very similar in this subsample as compared with the whole sample (highest concussion quartile: 25.0-fold greater risk of poor cognition-related QOL,

TABLE 4
 Risk of Indicators of Depression and Anxiety in Association
 With Number of Professional Seasons and Playing Position: Football Players Health Study (n = 3484)^a

	Risk Ratio (95% CI)					
	Indicators of Depression			Indicators of Anxiety		
	Model 1a ^b	Model 2a: Model 1a ^c	Model 3a: Model 2a ^d	Model 1b ^b	Model 2b: Model 1b ^c	Model 3b: Model 2b ^d
NFL seasons (per 5 seasons)	1.09 (1.00-1.18)	0.98 (0.90-1.06)	0.95 (0.87-1.03)	1.04 (0.96-1.13)	0.93 (0.86-1.01)	0.90 (0.84-0.97)
Position						
Kicker/punter	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Quarterback	1.21 (0.66-2.22)	0.93 (0.51-1.70)	0.92 (0.50-1.69)	0.97 (0.56-1.69)	0.74 (0.43-1.28)	0.74 (0.43-1.28)
Wide receiver	1.19 (0.69-2.05)	0.76 (0.45-1.30)	0.77 (0.46-1.38)	1.28 (0.80-2.05)	0.81 (0.51-1.27)	0.82 (0.52-1.31)
Tight end	1.28 (0.74-2.24)	0.80 (0.46-1.38)	0.79 (0.46-1.38)	0.93 (0.56-1.54)	0.56 (0.34-0.92) ^e	0.56 (0.34-0.92) ^f
Running back	2.07 (1.23-3.49) ^e	1.13 (0.67-1.89)	1.13 (0.67-1.90)	1.82 (1.15-2.89) ^f	0.96 (0.61-1.51)	0.96 (0.61-1.51)
Offensive line	1.68 (1.01-2.79)	1.01 (0.61-1.67)	0.98 (0.58-1.63)	1.47 (0.95-2.27)	0.85 (0.55-1.31)	0.82 (0.53-1.28)
Linebacker	1.50 (0.90-2.52)	0.81 (0.48-1.36)	0.81 (0.48-1.36)	1.28 (0.82-2.01)	0.66 (0.43-1.04) ^f	0.66 (0.42-1.04)
Defensive back	1.36 (0.81-2.30)	0.82 (0.49-1.37)	0.84 (0.50-1.43)	1.26 (0.80-1.99)	0.73 (0.47-1.15)	0.76 (0.48-1.20)
Defensive line	1.91 (1.14-3.19) ^f	1.11 (0.67-1.85)	1.10 (0.65-1.84)	1.57 (1.00-2.45) ^f	0.88 (0.57-1.37)	0.87 (0.55-1.35)
Special teams						
Did not play often	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Strength	1.08 (0.84-1.39)	0.98 (0.78-1.24)	0.98 (0.78-1.24)	1.20 (0.95-1.51)	1.08 (0.88-1.34)	1.09 (0.89-1.34)
Speed	0.97 (0.82-1.14)	0.92 (0.79-1.08)	0.92 (0.79-1.07)	0.97 (0.83-1.14)	0.99 (0.99-1.00)	0.93 (0.80-1.07)
Concussion symptoms during playing years						
Quartile 1		1.0 (Reference)	1.0 (Reference)		1.0 (Reference)	1.0 (Reference)
Quartile 2		2.22 (1.67-2.94) ^g	2.12 (1.60-2.82) ^g		2.17 (1.65-2.86) ^g	2.08 (1.58-2.75) ^g
Quartile 3		3.70 (2.85-4.82) ^g	3.42 (2.63-4.46) ^g		3.80 (2.94-4.90) ^g	3.51 (2.72-4.54) ^g
Quartile 4		6.01 (4.67-8.74) ^g	5.31 (4.10-6.87) ^g		6.41 (5.02-8.19) ^g	5.65 (4.40-7.26) ^g

^aMen were considered to have indicators of depression if they had a score ≥ 3 on the Patient Health Questionnaire–2 or current antidepressant use. Men were considered to have indicators of anxiety if they had a score ≥ 3 on the Generalized Anxiety Disorder Scale–2 or current anti-anxiety medication use. NFL, National Football League.

^bAdjusted for age at questionnaire and race.

^cFurther adjusted for concussion symptoms during playing years.

^dFurther adjusted for pain medication and surgery during playing years.

^e $P < .01$.

^f $P < .05$.

^g $P < .001$.

5.9-fold greater risk of depression, and 6.1-fold greater risk of anxiety, all $P < .0001$).

Age at first organized football was not associated with cognition-related QOL, depression, or anxiety, whether continuously or dichotomized at <12 years (age <12 years: poor Neuro-QOL: RR, 1.05; 95% CI, 0.88-1.26; depression: RR, 1.00; 95% CI, 0.89-1.13; anxiety: RR, 1.04; 95% CI, 0.93-1.17; all $P > .05$). In analyses exploring potential effects of participation bias, results were nearly identical in models weighted and not weighted for the inverse probability of participation.

DISCUSSION

We found that each 5 seasons of professional play was associated with 19% greater risk of poor cognition-related QOL. Among men who played only 1 season in the NFL, 5.8% had poor cognition-related QOL versus 12.7% in men with >1 season, again suggesting that professional play

placed players at increased risk, over and above risk resulting from college and youth football. Regarding individual positions, running backs and defensive linemen were at elevated risk of all 3 outcomes that we examined, as compared with kickers and punters. In addition, we found that players in positions with medium or high mean concussion symptoms per season had greater risk of all 3 outcomes as compared with players in positions with low mean concussion symptoms (ie, kickers, punters, and quarterbacks). Concussion symptoms at the time of head impact accounted for differences in cognition-related QOL and depression by playing seasons and by position, both individually and grouped, suggesting that experience of concussions underlies much of the association of NFL seasons and playing position with the outcomes.

Concussion symptoms and loss of consciousness were strongly associated with indicators of anxiety and depression, even decades after the injury. To our knowledge, only 3 large- or moderate-sized studies have examined depression,^{17,24,26} and no studies have examined anxiety

TABLE 5
Association of Position Group With Cognition-Related QOL and Indicators of Depression and Anxiety^a

Position Concussion Risk	Poor Cognition-Related QOL		Indicators of Depression		Indicators of Anxiety	
	Model 1a ^b	Model 2a: Model 1a ^c	Model 1b ^b	Model 2b: Model 1b ^c	Model 1c ^b	Model 2c: Model 1c ^c
Low	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Medium	1.72 (1.03-2.88) ^d	0.93 (0.57-1.52)	1.39 (1.02-1.89) ^d	1.00 (0.75-1.36)	1.39 (1.03-1.86) ^d	0.96 (0.73-1.27)
High	2.23 (1.33-3.73) ^e	1.03 (0.62-1.68)	1.41 (1.03-1.94) ^d	0.94 (0.70-1.27)	1.45 (1.08-1.95) ^d	0.92 (0.69-1.22)

^aPositions were grouped according to mean concussion symptoms per season for each position across all players in that position: low (≤ 2 symptoms/season: kickers, punters, and quarterbacks), medium (> 2 to 3.4 symptoms/season: wide receivers, defensive backs, linemen, tight ends), and high (> 3.4 symptoms/season: running backs, linebackers, special teams). NFL, National Football League; QOL, quality of life.

^bAdjusted for seasons in NFL, age at questionnaire, and race.

^cFurther adjusted for concussion symptoms during playing years.

^d $P < .05$.

^e $P < .01$.

TABLE 6
Loss of Consciousness During Football in Association With Cognition-Related Quality of Life and Indicators of Depression and Anxiety: Football Players Health Study (n = 3394)^a

Loss of Consciousness During Playing Years	n	Risk Ratio (95% CI)		
		Poor Cognition-Related Quality of Life	Indicators of Depression	Indicators of Anxiety
Analysis 1: Entire cohort				
Never	1631	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Once	760	1.67 (1.28-2.18) ^b	1.39 (1.17-1.65) ^b	1.26 (1.07-1.48) ^c
2-5	810	2.54 (2.01-3.21) ^b	2.08 (1.79-2.40) ^b	1.87 (1.63-2.15) ^b
6-10	110	4.87 (3.52-6.72) ^b	3.28 (2.68-4.03) ^b	2.71 (2.20-3.33) ^b
≥ 11	83	6.15 (4.60-8.21) ^b	3.59 (2.95-4.36) ^b	3.39 (2.84-4.05) ^b
Analysis 2: Men who last played football ≥ 20 y prior (n = 1863)				
Never	800	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Once	440	1.41 (0.96-2.06)	1.38 (1.08-1.76) ^d	1.29 (1.02-1.64) ^d
2-5	519	2.28 (1.65-3.14) ^b	2.02 (1.64-2.49) ^b	1.84 (1.50-2.25) ^b
6-10	63	5.65 (3.71-8.63) ^b	3.43 (2.52-4.68) ^b	2.73 (1.95-3.81) ^b
≥ 11	41	4.91 (3.10-7.78) ^b	3.69 (2.72-5.02) ^b	3.79 (2.91-4.94) ^b

^aAll models adjusted for age at questionnaire and race. Poor cognition-related quality of life was defined as a Neuro-QOL score ≤ 2 SD below the US population mean. Men were considered to have indicators of depression if they had a score ≥ 3 on the Patient Health Questionnaire-2 or current antidepressant use. Men were considered to have indicators of anxiety if they had a score ≥ 3 on the Generalized Anxiety Disorder Scale-2 or current antianxiety medication use. Neuro-QOL, Quality of Life in Neurological Disorders: Applied Cognition-General Concerns.

^b $P < .001$.

^c $P < .01$.

^d $P < .05$.

symptoms in association with concussion at long periods after injury. Existing studies typically examined symptoms within 1 year of injury,^{25,46} lacked nonconcussed comparison groups,^{25,31} or had unknown time between injury and psychiatric symptoms, with few exceptions.¹⁵ Our results suggest that anxiety and depression may be important long-term sequelae of concussion.

Age at which organized football was first played was not associated with cognition-related QOL, depression, or anxiety. Prior studies found associations of cognitive impairment and corpus callosum microstructure with young age at first organized football, but these were small- or moderate-sized

convenience samples ($N \leq 42$, $N = 214$).^{1,49,50} However, when compared with typical youth sports participants, former professional athletes are likely to have played youth sports with unusual intensity (eg, playing as a starter, having more game time, playing more seasons of sports across childhood) and hence may not be representative. In addition, for professional athletes, the effects of youth sports could be overpowered by subsequent professional exposures, and children more affected by injury would likely not continue to professional competition, possibly creating bias. Thus, former professional athletes are not ideal for the study of effects of youth sports.

Our study has important limitations. First, although the Neuro-QOL is a validated measure of cognition-related QOL,¹⁰ given recent public attention regarding the association of concussion with later-life cognitive function, it is possible that players who experienced concussions are sensitized to possible cognitive symptoms and may overreport them, but this would not affect associations of cognitive function with seasons or position of play. Second, our football measures were of events that, for some men, occurred many years ago. Therefore, they are subject to recall bias. In particular, concussion symptoms may be difficult to accurately recollect. However, we also queried loss-of-consciousness events, which may be easier to recollect, and had similar findings. Third, we were unable to consider possible effects of subconcussive blows, which may be associated with cognitive function, although findings are mixed.⁸ Fourth, estimates of the association between seasons of play and neuropsychiatric outcomes are likely biased by the healthy worker effect.¹¹ Players who remain in the NFL for many years are often those who have not been seriously injured.⁵¹ This situation would bias effect estimates toward the null hypothesis; that is, our findings would be underestimates of true associations between seasons of play and health outcomes. Players may also have chosen or been unable to participate owing to ill health or death from football-related exposures, which would reduce prevalence estimates.³³ Fifth, our questionnaire response rate was modest and could have been affected by participation bias. In fact, in comparisons with data from Pro Football Reference, participants in the FPHS played more seasons, began their career earlier, and were more likely to be offensive linemen. However, participation bias could not account for our findings unless it was jointly related to both exposure and outcome.²² Additionally, results were very similar in analyses weighted for the probability of participation.

Concussion history and life in football appear to be associated with cognitive and mental health complaints. Further efforts to reduce risk are warranted, and an enhanced mechanistic understanding of risks and ways to mitigate risk is needed. Active players, with the medical professionals who care for them, might consider their future health in deciding whether to continue a football career after concussion.

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