# Lead toxicity from retained bullet fragments: A systematic review and meta-analysis

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**BACKGROUND:** Firearm injury remains a public health epidemic in the United States. A large proportion of individuals with gunshot wounds subsequently have retained bullet fragments (RBF). There are no standard medical guidelines regarding bullet removal and the full extent of the consequences of RBF remains unknown.

**OBJECTIVE:** To determine whether there is an association among RBF, elevated blood lead levels (BLL) and lead toxicity in survivors of firearm injury 16 years and older.

**METHODS:** PubMed, EMBASE, CINAHL, Scopus, Cochrane Library, and Sociological Abstracts electronic databases were searched for all randomized controlled trials, prospective and retrospective cohort, case-control and cross-sectional studies published in the English language between 1988 and 2018. Quality assessment and risk of bias was evaluated using the Newcastle Ottawa Scale. A meta-analysis was performed using a random-effects model.

**RESULTS:** The search yielded 2,012 articles after removal of duplicates. Twelve were included after full article review. Eleven studies supported an association between elevated BLL and RBF. Bony fractures were associated with increased risk of elevated BLL in three studies. A positive relationship between BLL and the number of RBF was also shown in three studies, with one study demonstrating 25.6% increase in BLL for every natural-log increase in RBF (1–228, $p < 0.01$). Meta-analysis demonstrated BLL significantly higher in individuals with RBF as compared to controls (5.47 μg/dL, $p < 0.01$).

**CONCLUSION:** Patients with bony fractures or multiple RBF, who are at higher risk of elevated BLL, should be monitored for BLL in intervals of 3 months within the first year of injury. For patients who return with BLL above 5 μg/dL, all efforts must be undertaken to remove fragments if there is no potential to worsen the injury. (*J Trauma Acute Care Surg.* 2019;87: 707–716. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

**LEVEL OF EVIDENCE:** Systematic review, Meta-analysis, level III.

**KEY WORDS:** Lead; plumbism; retained bullet; gunshot injury.

Firearm injury remains a public health epidemic in the United States. According to the Centers for Disease Control and Prevention (CDC), there were more than 140,000 firearm injuries in 2016 of which more than 100,000 were nonfatal.[1] A large proportion of these patients have retained bullets or fragments (RBF) although the exact prevalence of RBFs remain unknown. In addition, there are no standard medical guidelines regarding RBF removal or management. A recent study identified bullet removal as indicated acutely for bullets in joints as well as the palm or sole but found no evidence providing rationale for routine bullet removal outside these anatomical locations.[2] Most institutions limit bullet removal to those found in joints, cerebrospinal fluid (CSF), the globe of the eye, or bullets leading to significant morbidity or symptoms.[3] Otherwise, most clinicians do not routinely remove bullets, often quoting the difficulty in finding the bullet and other risks of surgical intervention. Additionally, in the acute phase of traumatic injury, managing the damage caused by the bullet tract is often more critical than removal of the bullet itself. As a result, there are many victims of nonfatal firearm injury with RBF and little available knowledge regarding the potential long-term psychological and physical consequences.

Lead toxicity is one potential complication of RBF that has been discussed in multiple case reports.[4] Indeed, the documented increased risk of lead toxicity from bullets exposed to synovial fluid or CSF is the driving force behind early removal of these bullets.[3] Clinicians have otherwise assumed RBF in tissue have a low risk of systemic lead dispersion due to the formation of encapsulating scar tissue. There are also multiple case reports, however, describing severe lead toxicity from extra-articular retained bullets found in soft tissue.[5–7] In these cases, the clinical signs and symptoms of lead toxicity are subtle and go undetected for years, leading to lead intoxication being reported as a late indication for bullet removal.[2] This raises the question as to whether individuals with RBF may have an elevated blood lead levels (BLL) without exhibiting any clinical symptoms.

In 2015, the CDC decreased the threshold for the definition of elevated BLL from 10 μg/dL or greater to 5 μg/dL or greater, given data showing that even lower BLL may have adverse health effects. Preliminary searches on the topic of BLL and lead toxicity symptoms as related to RBF revealed an absence of a systematic review on this topic. The purpose of this review is to systematically examine and aggregate existing studies on this subject and gain better insight into whether RBF after

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firearm injury are associated with elevated BLL and symptoms of lead toxicity. Understanding the potential association of RBF and lead poisoning may assist in defining guidelines regarding bullet removal and in developing strategies for injury prevention and patient care.

# METHODS

## Eligibility Criteria

All observational cohort, case-control and cross-sectional studies reporting data on BLL or lead toxicity signs or symptoms in the context of firearm injury and RBF were considered eligible for inclusion. Randomized controlled trials (RCTs) were not expected due to ethical considerations and case-reports and case-series were excluded due to their weaker validity. Studies were excluded if they did not contain data on adults, were not published in the English language, or were not performed on human subjects. The review was originally planned to limit studies to cases 18 years or older, but this was adjusted to include studies with data on cases 16 years and older to expand eligible studies. The study was limited to a publication date range of 30 years from June 16, 1988, to June 15, 2018.

## Data Sources and Search Strategy

Using the Patient/Population, Intervention, Comparison, Outcome format, we searched PubMed, EMBASE, CINAHL, Scopus, Cochrane Library, and Sociological Abstracts electronic databases for all RCTs, prospective and retrospective cohorts, case-control and cross-sectional studies published in the English language between 1988 and 2018 using the following search strategy developed with the assistance of an experienced librarian (K.B.): "Lead poisoning OR toxicity AND complications OR prognosis OR mortality" AND "retained bullet OR gunshot OR foreign bodies." References of included studies were screened for pertinent articles to ensure a thorough and complete review.

## Study Selection

The screening and selection of studies was performed according to the PRISMA 2009 Statement (see Fig. 1).[8] Records

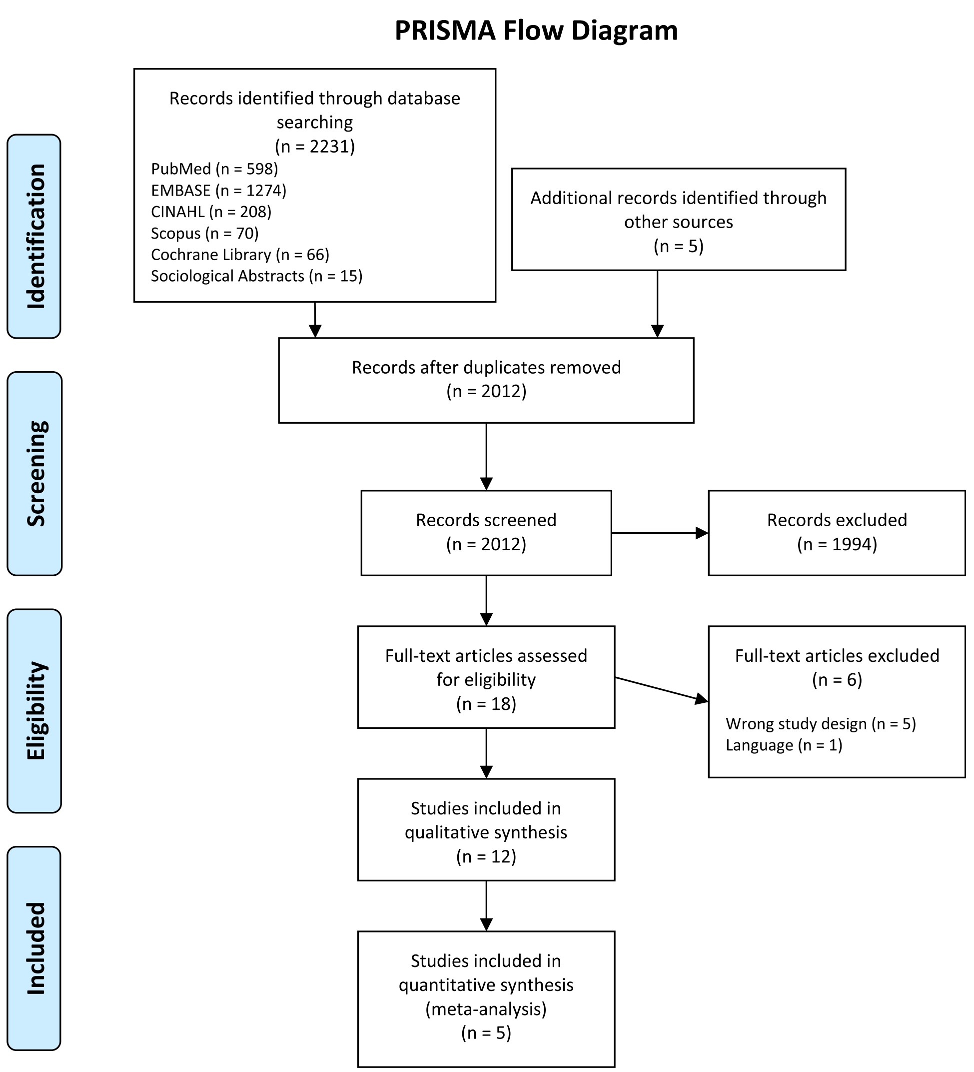


**Figure 1.** Study flowchart.

**TABLE 1.** Study Characteristics

| Study | Design | Country | Age, y | Sample Size | RBF Specifications | BLL Measurement | Primary Outcome | Secondary Findings | Level of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| Alarcon et al., 2009[12] | Cross-sectional | United States | 16+ | 1,060 | — | BLL ≥ 20 and ≥40 µg/dL prevalence 2005–2007. | RBF-associated cases accounted for 82 (7.7%) | Among RBF-associated cases, 29 (35%) adults had BLL ≥ 40 µg/dL. | IV |
| Alarcon et al., 2011[13] | Cross-sectional | United States. | 16+ | 665 | — | BLL ≥ 25 and BLL ≥ 40 µg/dL prevalence 2008–2009. | RBF-associated cases accounted for 49 (7.3%). | Among RBF-associated cases, 15 (30%) adults had BLL ≥ 40 µg/dL. | IV |
| de Araújo et al., 2015[14] | Case-control | Brazil | 19+ | 90 | RBF retained for at least 6 months; confirmed by radiography | Whole BLL | RBF-associated cases had higher BLL averages (9.01 µg/dL vs. 2.17 µg/dL) than the control group ($p < 0.01$).<br>Higher number of symptoms* in RBF-associated cases. | Weak negative correlation between RBF duration and BLL.<br>No relation between RBF duration and symptom frequency.<br>No relation between BLL and RBF location. | III |
| Edetanlen and Saheeb, 2016[15] | Prospective cohort | Nigeria | 19+ (19–65) | 52 | RBF from craniomaxillofacial gunshot injury; confirmed by radiography | Whole BLL 3 days and 3 months postinjury | RBF-associated BLL was higher at 3 days and 3 months postinjury (0.11 vs. 0.03, 0.30 vs. 0.02 µmol/L, $p < 0.01$). | Positive correlation between the number of RBF and BLL concentrations. | II |
| Farrell et al., 1999[16] | Case-control | United States | 18+ (31–74) | 30 | Confirmed by radiography | Whole BLL | RBF-associated cases had higher mean whole BLL (17 vs. 7 µg/dL) than the control ($p = 0.002$). | Among cases, 4/15 (27%) reported lead toxicity symptoms – all reported GI disturbances and two reported neurological disturbances. | III |
| McQuirter et al., 2001[17] | Prospective cohort | United States | 18+ | 48 | Confirmed by radiography | Whole BLL at admission or 6 months postinjury and 5 to 234 d after. | Mean BLL increased with time (5.1 vs. 7.7 µg/dL, $p = 0.001$). | BLL increased with RBF duration and rise is enhanced in presence of fracture ($p < 0.01$). | II |
| McQuirter et al., 2004[18] | Prospective cohort | United States | 7+ y; 20.6% were 18 y or younger | 451 | Confirmed by radiography | Whole BLL at intervals within 12 months postinjury; BLL ≥ 20 µg/dL at 3 and 6 months postinjury; BLL ≥ 10 µg/dL at 12 months postinjury. | Prevalence of BLL ≥ 10 µg/dL and 20 µg/dL increased time after 3 months (2.1% and 0.2% to 38.1% and 11.8%). Prevalence of BLL ≥ 10 µg/dL and 20 µg/dL declined from at 12 months (38.1% and 11.8% to 20.1% and 2.6%). | Cases with RBF near bone had 32% higher BLL ($p < 0.0005$) and those near joints had 17% higher ($p = 0.032$).<br>Increasing age (9–70 y) and increasing RBF numbers (1–228) were associated with increased BLL ($p < 0.0005$).<br>Increased number of RBF, torso bone fractures and RBF in humerus in conjunction predicted elevated BLL. | I |

*Continued next page*

**TABLE 1.** *(Continued)*

| Study | Design | Country | Age, y | Sample Size | RBF Specifications | BLL Measurement | Primary Outcome | Secondary Findings | Level of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| Moazeni et al., 2014[19] | Case-control | Iran | 18+ (22–49) | 50 | Confirmed by radiography | Whole BLL | No significant difference in BLL in RBF-cases vs. controls (29 μg/dL vs. 25.3 μg/dL, $p = 0.3$). No difference in lead toxicity symptom frequency. | Positive association between serum lead level and number of RBF ($r = 0.447$ and $p = 0.025$). No relation of RBF duration and BLL. | IV |
| Nguyen et al., 2005[20] | Case-control | United States | 18+ | 240 | Extra-articular missiles (EARM); confirmed by radiography. | Whole BLL *Controls matched for external exposures for lead | RBF-associated cases had higher mean whole BLL than controls (6.7 vs. 3.61 μg/dL, $p < 0.01$). No difference in number of reported lead toxicity symptoms | Longer duration of RBF was not associated with higher BLL. Fractures were associated with elevated BLL.<br>No correlation between number of reported lead toxicity symptoms and whole BLL. | III |
| Roscoe and Graydon, 2004[21] | Cross-sectional | United States | 16+ | 338 | Retained bullets or gunshot wounds | BLL ≥ 25 μg/dL | RBF-associated cases accounted for 36 (11%) adults with BLLs ≥25 μg/dL in 2002. | — | IV |
| Roscoe and Graydon, 2006[22] | Cross-sectional | United States | 16+ | 842 | Retained bullets or gunshot wounds | BLL ≥ 25 μg/dL | RBF-associated cases accounted for 5% adults with BLLs ≥25 μg/dL from 2003 to 2004. | — | IV |
| Weiss et al., 2017[23] | Cross-sectional | United States | 16+ | 145,811 | — | BLL ≥ 10 μg/dL | RBF-associated cases accounted for 457 (0.3%) adults with BLLs ≥10 μg/dL from 2003 to 2012. | RBF-associated cases accounted for a higher percentage of adults (17, 4.9%) with BLLs ≥80 μg/dL from 2003 to 2012.<br>RBF-associated elevated BLLs occurred primarily among males 16–24 y, as compared with non–RBF-associated cases, which primarily occurred males of 35–44 y | IV |

*Symptoms: memory loss, irritancy, weakness, trembling, tingling limbs, bad mood, joints pain, myalgia, daylight drowsiness, abdominal pain ($p < 0.05$).

identified through database searches were first screened for duplicates through the assistance of EndNote software. The remaining titles and/or abstracts were screened independently by two authors (A.A and R.N.S.) with the assistance of Rayyan software,[9] to determine potentially relevant articles. If either reviewer determined an article to be relevant based on title and/or abstract, the full text article was retrieved and independently reviewed for eligibility by A.A. and R.N.S. Any discrepancies between reviewers were resolved through discussion.

## Data Extraction

One review author (A.A.) manually extracted data from included studies into Excel. Data abstracted included study setting, demographic information, methodology, intervention details, all reported patient-important outcomes and information for assessment of study quality and risk of bias. Primary outcomes of interest were BLL and symptoms of lead toxicity.

## Assessment of Risk of Bias

Quality assessment was initially planned using the Grades of Recommendation, Assessment, Development and Evaluation approach; however, in-depth analysis of identified studies revealed substantial heterogeneity necessitating the use of an alternative assessment tool aimed at individual study quality. The Newcastle-Ottawa Scale Quality Assessment Scale (NOS), a tool identified by the Cochrane Handbook[10] as a valid quality assessment and risk of bias evaluation tool for nonrandomized studies, was used in its place. Newcastle-Ottawa Scale Quality Assessment Scale evaluates studies based on the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. A modified NOS was used for evaluation of cross-sectional studies. Risk of bias across meta-analysis studies was assessed through use of a funnel plot.

## Data Synthesis and Analysis

A meta-analysis using a random-effects model was performed to compare continuous data by difference in means and standard deviation in BLL of individuals with RBF to BLL of individuals without RBF. Five of 12 studies were included. Studies were included in the meta-analysis based on comparability of study design. Seven studies were excluded on the premise that they lacked a control group, which is a necessary component for statistical analysis. Analyses were performed with the assistance of Review Manager 5.3. For heterogeneity, the $I^2$ test of Higgins et al.[11] and the $\chi^2$ test were used.

# RESULTS

Our search yielded 2,012 articles after duplicates were excluded. Twelve were included after full article review. All studies were observational—there were five cross-sectionals, four case-controls, and three prospective cohorts (see Table 1). Sample size varied from 15 to 120 with a median of 26 patients. Three prospective studies provide Level I-II evidence. Four case-control studies provide Level III-IV evidence. Five cross-sectional studies provide Level IV evidence. As expected, no randomized studies were available. Meta-analysis was performed on four case-control studies and one prospective cohort study. Higgins et al. tests for heterogeneity resulted in an $I^2$ of 74% and test and $\chi^2$ of 15.24 with df of 4 ($p = 0.004$), indicating significant statistical heterogeneity among studies and leading to the use of a random-effects model for effect analysis. Figure 2 summarizes the meta-analysis results. A quality analysis and risk of bias evaluation was performed using the NOS (see Table 2). The population was well selected in nine of 12 studies. All studies screened for exposure to lead occupation. Comparability was nonexistent in two prospective studies without control groups and therefore these studies and cross-sectional studies were excluded from the meta-analysis. Risk of bias across studies in

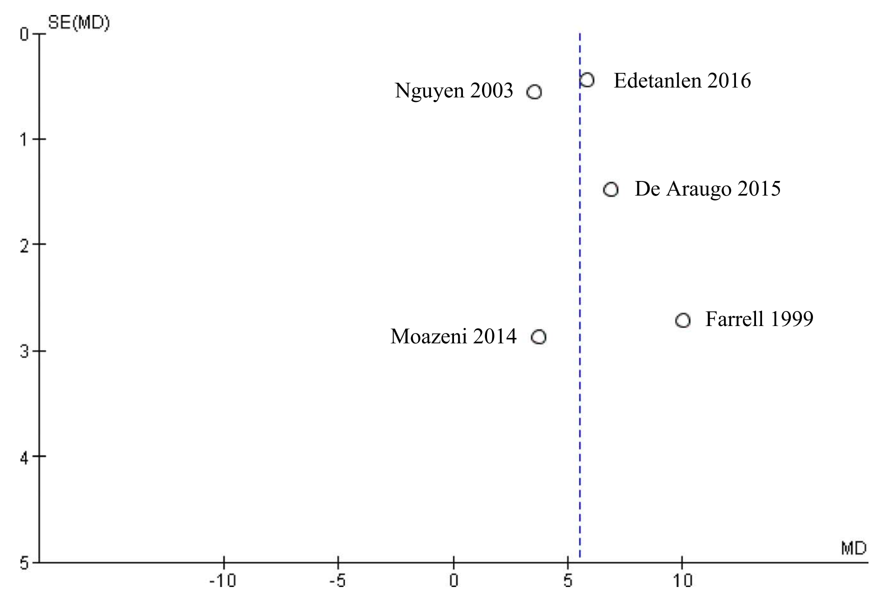


**Figure 2.** Funnel plot. Comparison of outcome: BLLs (µg/dL).

 

**TABLE 2.** Quality Assessment and Evaluation of Risk of Bias Using the Newcastle-Ottawa Scale

| Study | Study Design | Selection | Comparability | Exposure/Outcome |
|---|---|---|---|---|
| Alarcon et al., 2009[12] | Cross-sectional | **** | * | *** |
| Alarcon et al., 2011[13] | Cross-sectional | **** | * | *** |
| de Araújo et al., 201514 | Case-control | *** | ** | *** |
| Edetanlen and Saheeb, 2016[15] | Prospective cohort | ** | ** | *** |
| Farrell et al., 1999[16] | Case-control | ** | ** | *** |
| McQuirter et al., 2001[17] | Prospective cohort | **** | — | *** |
| McQuirter et al., 2004[18] | Prospective cohort | **** | — | *** |
| Moazeni et al., 2014[19] | Case-control | **** | ** | *** |
| Nguyen et al., 2005[20] | Case-control | ** | ** | *** |
| Roscoe and Graydon, 2004[21] | Cross-sectional | **** | * | *** |
| Roscoe and Graydon, 2006[22] | Cross-sectional | **** | * | *** |
| Weiss et al., 2017[23] | Cross-sectional | **** | * | *** |

Selection: maximum of 4 stars (****).
Comparability: maximum of 2 stars (**).
Exposure/Outcome: maximum of 3 stars (***).

the meta-analysis was assessed through a funnel plot (see Fig. 2), showing minimal evidence of publication bias.

## Elevated BLLs

Eleven (92%) studies show evidence supporting an association between elevated BLL and RBF after firearm injury. Two cross-sectional studies examining the prevalence of individuals with RBF among state-reported BLL of 25 μg/dL or greater ranged from 5% to 11% with a median of 7.5%. Both studies also reported a higher percentage of RBF-associated cases (30–35%) with BLL of 40 or greater. A third cross-sectional examining all reported RBF-associated cases between 2003 and 2012 reports 0.3% prevalence for BLL of 10 μg/dL or greater and 4.9% for BLL of 80 μg/dL or greater, with the majority of BLL (59.1%) within the 10 μg/dL to 24 μg/dL range.

Three case-control studies[14,16,20] demonstrated RBF-associated cases with significantly higher BLL averages than control groups, although that degree of variation ranged from 3.09 μg/dL to 10 μg/dL, with a median of 6.84 μg/dL. On the contrary, a fourth case-control study[19] showed no significant difference in BLL between RBF cases and controls (29 μg/dL vs. 25.3 μg/dL, $p = 0.3$), although overall BLL were higher (14.5–71.5 μg/dL). All three prospective studies examined BLL over time and demonstrated a positive relationship within the first 3 months of injury.[15,17,18]

## The Effect of Bony Fractures

Three (25%) studies associated bony fractures with increased risk of elevated BLL in individuals with RBF.[17,18,20] Nguyen et al. demonstrated a mean BLL of 9.95 μg/dL in individuals with fractures versus those without (6.23 μg/dL). The McQuirter et al. 2004 study identified torso bone fractures in conjunction with increased number of RBF and RBF in the humerus as predictors of elevated BLL while also showing that individuals with torso bone fracture had BLL 29.5% higher than those without. The McQuirter et al. 2001 study identified the presence of a bone fracture as a factor contributing to significant rises in BLLs overtime ($F_{1,22} = 6.225$, $p = 0.021$).

## The Effect of Number of RBF

Three studies examined the relationship between number of RBF and BLL and all demonstrated a positive association.[15,18,19] Edetanlen et al. grouped their findings into 5 RBF or less, 6 to 9 RBF, and 10 RBG or greater ($r = 0.754$, $p < 0.01$). McQuirter et al. used a mixed model fixed effect estimate to compare natural logs of blood lead concentration and number of RBF, ranging from 1 to 228 fragments, and found that BLL concentration increased with number of RBF by 25.6% for every natural-log increase in RBF number (1 to 2.7, 2.7 to 7.4, etc.). Moazeni et al. also demonstrated a positive association between serum lead level and number of RBF ($r = 0.447$ and $p = 0.025$); however, a range of RBF was not provided.

## The Effect of RBF Duration

Six studies examined the relation of RBF duration and BLL.[14,15,17–20] de Araújo et al. found a weak negative correlation. Edetanlen et al. demonstrated an increase in BLL in RBF-associated cases from 3 days to 3 months postinjury (0.11 to 0.30 μmol/L). McQuirter et al. 2001 data also showed an increase in mean BLL with time (5.1 μg/dL vs. 7.7 μg/dL, $p = 0.001$), with further analysis revealing a greater increase in the presence of a fracture. This study evaluated BLL at two measurements between the day of admission to 234 days postinjury and significant variation between these intervals is likely. The subsequent study by McQuirter et al. in 2004 examining the prevalence of BLL of 10 μg/dL or greater and 20 μg/dL found that BLL peaked at 3 months and declined by 12 months. The two studies by Moazeni et al. and Nguyen et al. did not show any relation between RBF duration and BLL.

## The Effect of RBF Location

Two studies examined the relationship between RBF location and BLL.[15,18] McQuirter et al. demonstrated that cases with RBF near bone had 32% higher BLL ($p < 0.0005$) and cases with RBF near joints had 17% higher ($p = 0.032$). The same study specifically identified RBF in the humerus as a predictor of elevated BLL. The de Araújo et al. study showed no relation between BLL based on RBF location.

## Lead Toxicity Symptoms

Four studies included lead toxicity symptom frequency as an outcome.[14,16,19,20] Half reported increased frequency of lead toxicity symptoms among RBF-associated cases and half noted no significant difference. de Araújo et al. found a significantly higher frequency of memory loss, irritancy, weakness, trembling, tingling limbs, bad mood, joints pain, myalgia, daylight drowsiness and abdominal pain ($p < 0.05$) among RBF-associated cases but did not find any relation to RBF duration. In the Farrell et al. study, 27% of the RBF-associated cases reported gastrointestinal and neurological disturbances. The Moazeni et al. case-control study did not identify any difference in reported lead toxicity symptoms between cases and controls, although neither group reported any symptoms. In addition to showing no difference in reported lead toxicity symptoms, the Nguyen et al. study also demonstrated no correlation between the number of reported lead toxicity symptoms and BLL.

## Meta-Analysis

Meta-analysis of a pooled sample size of 462 demonstrated a significantly higher BLL by 5.47 μg/dL (3.70, 7.24 μg/dL) in individuals with retained bullets as compared with the control group ($p < 0.01$). Median BLL was 9.01 μg/dL (see Fig. 2). A random-effects model was used for effect analysis due to Higgins et al. tests for heterogeneity demonstrating significant statistical heterogeneity among studies ($I^2 = 74\%$, $\chi^2 = 15.24$, df = 4, $p = 0.004$) (see Fig. 3).

# DISCUSSION

In this review, we present the aggregation and analysis of 12 systematically identified studies on the association of RBF from firearm injury and BLL and lead toxicity symptoms in individuals of 16 years and older. We also examined the effect of RBF number, duration, and location on these outcomes.

With regard to the primary outcome, the results of the meta-analysis and qualitative evaluation both showed an association of RBF with elevated BLL. Meta-analysis demonstrated that the mean BLL of individuals with RBF was higher by 5.47 μg/dL as compared with the control, which was statistically significant. The median BLL was 9.01 μg/dL, which exceeds the updated CDC definition of elevated BLL of 5 μg/dL or greater. Two studies in the meta-analysis had an RBF-associated mean BLL exceeding 10 μg/dL, as did multiple studies not included in the meta-analysis. One of the cross-sectional studies showed RBF-associated BLL ranging from 10 to greater than 300 μg/dL, however the majority of BLLs were recorded as 10 μg/dL to 24 μg/dL.[6] Unlike the previously mentioned case-reports of RBF and severe lead toxicity, the patients in this review better represent the average population of individuals with RBF from firearm injury. The aggregate of data from this review demonstrates that RBF are not only associated with BLL higher than the average BLL of adults in the United States of 3 μg/dL,[24] but are also associated with a level determined by the CDC as associated with adverse health effects.

Only two factors were identified in this review as independent predictors of elevated BLL: the number of RBF and the presence of bony fracture. The relation of number of RBF and BLL is discussed by McQuirter et al., who explains that since the bullets most frequently encountered by US civilian populations are made from a lead alloy or are clad bullets with a lead core, fragmentation of these bullets would increase surface area contact of lead with tissue. Either fragmentation of a single bullet or multiple bullets from multiple gunshot injuries could increase surface area contact with tissue. Interestingly, Edetanlen et al. hypothesize that bullets that strike bone stand a greater chance of fragmentation, which raises the question as to whether the presence of bone fractures and the number of RBF are truly independent predictors of elevated BLL.

While increased bullet fragmentation may play a role, the authors of the studies finding a positive association between BLL and the presence of bony fractures hypothesize that the elevated BLL may also be attributed to the return of lead to the systemic circulation through bone resorption activity by osteoclasts during the initial healing process.[17,18,20] This would also be consistent with the trend of BLL to peak within the first 3 months postinjury, when osteoclast resorption activity is at its highest. Since the half-life of lead in blood is approximately 35 days, in the absence of a bone fracture, the sensitivity of measuring BLL is limited by time elapsed since injury.[25] After initial exposure, bones become the primary site of lead storage in the human body and may be a better source to measure overall body lead burden.[25]

Measuring whole bone lead levels can be performed using a noninvasive x-ray fluorescence technique.[25] Only two studies in this review examined bone lead levels as an outcome.[17,18] McQuirter et al. demonstrated that individuals with higher bone lead levels had greater increases in BLL over time as compared with individuals with lower bone lead levels.[17] This supports the idea that overall body lead burden may impact overall exposure to lead, most likely through slow release from bone over time. This form of chronic lead toxicity could explain subclinical cases of lead toxicity in individuals with lower BLL and is worthy of further investigation.

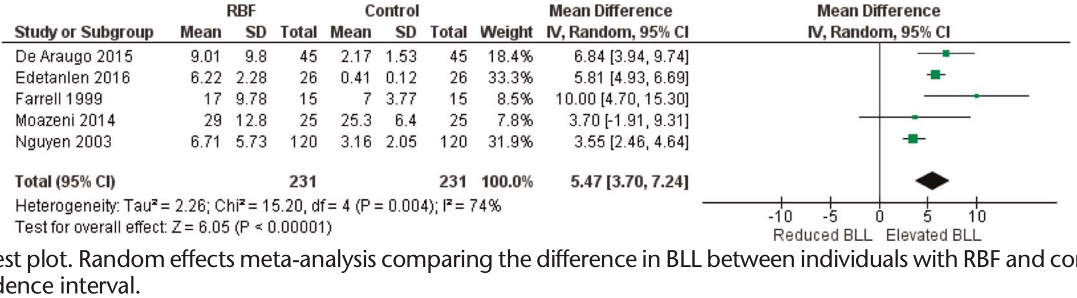


**Figure 3.** Forest plot. Random effects meta-analysis comparing the difference in BLL between individuals with RBF and controls without RBF. CI, confidence interval.

The studies in this review provided conflicting information regarding the influence of RBF duration and location on BLL. Among the six studies examining RBF duration, half showed a rise in BLL within the first 3 months of injury. The de Araujo et al. study, which found a weak decrease in BLL with RBF duration, might be explained by the fact that BLLs were only measured in individuals after 6 months of RBF duration. The McQuirter et al. 2004 study showed that while BLL peaked at 3 months, it started declining at 6 and 12 months, which is consistent with the findings of Araujo et al. This trend of BLL across time may be related to the inflammatory and remodeling activity in the area of injury. However, more evidence is needed to demonstrate this relationship.

Regarding RBF location, the positive association found by McQuirter et al. 2004 between RBF located near bone or joints and elevated BLL is consistent with case reports described in the literature. Also, while the study by de Araújo et al. showed no relation of BLL by RBF location, it excluded an outlier case with a multifragmentary knee fracture and intraarticular retained bullets with a BLL of 61.8 μg/dL. Ultimately, however, the results from this review on the association between RBF location and BLL were nonconclusive. This departs from the conventional belief that intraarticular RBF exposed to synovial fluid or CSF pose greater risk for lead dissolution and elevated BLL. Intraarticular RBF are thought to lead to greater dissolution into the bloodstream through initial solubilization of lead in the walls of the RBF by synovial fluid or CSF through an induced inflammatory response that increases systematic absorption.[26] This belief is largely theoretical and is based off case-reports.[27–30] To date, no animal studies have demonstrated a statistically significant association between RBF exposure to synovial fluid and CSF and elevated BLL.[31,32] Given that this is currently the only clear mandate for RBF removal, this potential relationship warrants further investigation.

Elevated BLL do not always correlate to clinical manifestation of lead toxicity through common symptoms. Only four studies provided insight into the relation of RBF to clinical lead toxicity symptom prevalence, and the results were nonconclusive. This raises the question as to whether the results of this review showing a statistically significantly higher BLL in individuals with RBF are also clinically significant. It should be noted that lead toxicity symptoms are often vague and nondescript, making the ability to capture their prevalence difficult when relying on patient reporting. Among the two studies showing a significantly higher number of symptoms in individuals with RBF, gastrointestinal and neurological disturbances were the primary symptoms. In the de Arujo et al. study, neurological disturbances included memory loss, irritancy and bad mood—all symptoms also commonly associated with psychological disease. These results align with a recent prospective study led by one of the authors (R.N.S.) demonstrating that RBF are associated with more severe depressive symptoms in victims of firearm injury.[33] While this outcome may be independent from the effects of elevated BLL and lead toxicity, it interesting to consider lead toxicity's potential role in the etiology of psychological symptoms in patients with RBF.

## Implications

Recent evidence has shown that BLLs as low as 5 μg/dL can have an impact on physical and psychological health. According to the CDC, BLLs of 5 μg/dL are associated with decreased renal function, and BLLs of 10 μg/dL are associated with increased blood pressure and hypertension.[34] The CDC also report a large body of evidence associating BLLs of 10 μg/dL with a reduction in IQ performance and other neuropsychological defects, including reduced hearing. Medium range BLLs of 15 μg/dL or greater have been associated with adverse effects on fertility.[35]

The results of this review demonstrate that it is important for clinicians to be aware of the possibility of clinical lead toxicity manifestation in patients who have been victims of firearm injury and may have RBF. Patients with bony fractures or multiple RBF, who are at higher risk of elevated BLL, should be monitored for BLL in intervals of 3 months within the first year of injury. For patients who return with BLL above 5 μg/dL, all efforts must be undertaken to remove fragments if there is no potential to worsen the injury. In all other patients, understanding the potential risks associated from elevated BLLs will help guide physicians toward identifying when bullet removal may be indicated as a part of recover. The potential for lead toxicity from RBF to manifest as psychological symptoms is of particular interest, considering that mental illness is associated with increased risks of injury recurrence.[36]

## Unanswered Questions and Future Directions

Existing studies demonstrate an association between RBF and increased BLL as compared with the general population; however, the clinical impact of this remains unclear. Furthermore, the level of evidence of studies included in this review is limited, and a stronger research is needed with prospective studies. Additional research examining bullet type and composition is needed to understand whether this has an impact on BLL. This is especially true as hollow-point bullets are becoming more commonplace than round-nose bullets. The traditional round-nose bullet core is made with lead or lead alloys, and may be covered by a metal jacket made of usually, cupronickel, brass, aluminum, or steel.[37] Hollow-point bullets have incomplete jackets that expose the end and allow for expansion of the bullet core upon impact. Theoretically, this may cause greater surface area contact of the lead core with tissue and increase risk of elevated BLL. The studies of this review did not differentiate bullet type and composition and this is a potential direction for future research. No database studies currently exist examining trends in the incidence and distribution of retained bullets in victims of firearm injury. Epidemiological studies like this may help provide insight into the potential impact of retained bullets on the health care system, including costs and rates of readmission. Understanding these patterns may additionally assist in defining guidelines regarding bullet removal and BLL monitoring. Further research could also provide insight into the role for whole bone lead level monitoring in patients with RBF.

## Limitations of the Review

The results of this review and meta-analysis are limited by a lack of stronger level evidence studies and the presence of substantial heterogeneity. The limitation to observational studies prevents the ability to establish causality and introduces greater risk for confounding by indication and selection bias. Threats to validity and precision from performance bias, detection bias, inadequate sample size, and lack of study efficiency, however, do not differ markedly in theory between RCTs and observational studies. Confounding by indication is a less significant problem in the included studies as they are not intervention-based, and knowledge of RBF status is independent of BLL measurements. Selection bias is reduced in these studies as all were screened for patients with potential occupational exposures to lead, the most common means of lead exposure in the United States,[35] although it should be noted that the Nguyen et al. study did not exclude these patients. Another potential source for selection bias, however, is the inclusion of only studies that measure lead levels. This would potentially miss studies associated with outcomes of individuals with RBF and unmeasured lower lead levels and further suggests the need for prospective studies.

Additionally, not all studies are representative of a general injured population as one study examined RBF resulting only from craniomaxillofacial firearm injury,[15] and another study only examined extra-articular RBF.[20] Some studies examined RBF-associated cases and BLL over a course of time, without a control comparison. Other studies examined the prevalence of RBF-associated BLL greater than a certain threshold at various points in time. Included studies may be influenced by performance bias in that there is little control over how individuals are exposed to their retained bullets. To account for this, most studies recorded data or performed subgroup analysis on details such as RBF number, duration and location. Another potential limitation of this study is that none the studies in this review differentiated bullet type and composition. This remains a difficult metric to assess, given that the circumstances of every patient's gunshot injury are not always known, and that unless the fragment is removed, we cannot be certain what metallic part of the bullet is/was retained in the body. Detection bias is limited in these studies by uniform measurement of BLLs across all by venipuncture and lead atomic absorption spectrophotometry. Reporting bias remains possible given that only one study demonstrated an insignificant relationship between RBF and BLL.

## AUTHORSHIP

A.A. participated in literature search, study design, data collection, data analysis, data interpretation, and writing. K.B. participated in study design. C.D. participated in critical revision. R.N.S. participated in literature search, study design, data collection and critical revision.

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## DISCLOSURES

There are no conflicts of interests by any of the authors to declare.

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