Orthopaedic corticosteroid injections and risk of acute coronary syndrome: a cohort study

INTRODUCTION
Intra-articular and soft-tissue corticosteroid injection (CSI) is a common treatment for arthritis and other inflammatory musculoskeletal conditions. In the US alone, several million injections are administered annually. CSIs are generally considered safe and effective, particularly in providing short-term symptom relief. Complications such as local trauma and infection have been reported, but their incidence is low.

The existence of serious endocrinological side effects from glucocorticoid steroid treatments was acknowledged soon after their introduction as a new and effective anti-inflammatory medication. Forty years later, Maxwell et al. raised the possibility that systemic corticosteroids also increase coronary heart disease. Corticosteroid treatment has been previously associated with risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and hyperglycaemia. Oral corticosteroid treatment may also be an independent risk factor for ischaemic events, particularly during treatment. To the best of the authors’ knowledge, however, the role of intra-articular and soft-tissue CSI as a potential risk factor for cardiovascular events has not been previously explored. Although hyperglycaemia and elevated blood pressure have been reported to occur in the hours after articular injections, several systematic reviews that considered the side effects of intra-articular and soft-tissue CSI did not mention ischaemic heart disease.

METHOD
Setting and data sources
Israel has a national health insurance scheme that guarantees medical care to all citizens through four healthcare providers, of which Clalit Health Services (CHS) is the largest. CHS members have

K Thomas, MBChB, MM, family physician, Department of Family Medicine, Tel Aviv University, Tel Aviv, Israel. Y Schonmann, MD, MSc, lead, Healthcare Quality Indicators Program for Clalit Health Services Hospitals, Department of Quality Measurements and Research, Clalit Health Services, Tel Aviv; Sial Research Center, Division of Community Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Address for correspondence
Katharine Thomas, Department of Family Medicine, Tel Aviv-Yafo and Dan Petach Tikva Districts, Clalit Health Services, Israel, and Department of Family Medicine, Tel Aviv University, Ramat Aviv PO Box 39400, Tel Aviv 6997801, Israel.

Email: marshylk@gmail.com

Submitted: 2 April 2020; Editor’s response: 13 May 2020; final acceptance: 9 July 2020.

©The Authors

This is the full-length article (published online 12 Jan 2021) of an abridged version published in print. Cite this version as: Br J Gen Pract 2021; DOI: https://doi.org/10.3399/bjgp20X713945
How this fits in

Intra-articular and soft-tissue corticosteroid injection (CSI) is a common treatment for orthopaedic conditions, often performed in primary care. CSIs are believed to have a low incidence of minor local side effects, and no known association with acute ischaemic cardiac events. This study suggests an increased incidence of acute coronary syndrome (ACS) in the week following CSI. The possible association of a common treatment and a life-threatening side effect is of importance to patients, clinicians, and policymakers.

comparable health characteristics with those of other healthcare providers,23,24 and the CHS population has been used as a proxy for the national population in various published reports.25–28 CHS has operated a centralised computerised personal medical file since the late 1990s, linking each patient’s individual national identity number with data from multiple sources, including primary care physicians, specialty clinics in the community, hospital records, laboratories, and pharmacies.29 This study was set in the orthopaedic clinic of the main CHS specialist consultation centre in Tel Aviv. The orthopaedic clinic is open 46 hours a week, and permanently staffed by eight orthopaedic specialists and a rotating staff of orthopaedic specialists from other clinics and hospitals who work on an ad hoc basis. Community-based orthopaedic consultations are a primary care service in Israel for which the majority of patients will have self-referred; a minority will have been referred by a different specialist or by their family physician. The orthopaedic consultation requires a small co-payment, and waiting lists are relatively short (a few days to several weeks). Orthopaedic specialists are reimbursed separately for office-based procedures like CSI (fee-for-service), based on the procedure codes that they record in the medical file. This file also allows the orthopaedic specialist access to the patients’ medical record including past medical history and medication use.

All patients aged ≥50 years who consulted with an orthopaedic specialist between 1 April 2012 and 31 December 2015 were included. The CHS chronic disease register was used to extract clinical information for the following conditions: smoking, ischaemic heart disease, hypertension, diabetes, hyperlipidaemia, obesity, and heart failure (see Supplementary Box S1 for details).29 CSI was considered to have been carried out during the orthopaedic consultation when the associated injection procedure code appeared in the medical file. During the study period the only non-corticosteroid product available for orthopaedic injections was the hyaluronic acid Arthrease®. Patients who had filled an Arthrease® prescription during the week before their orthopaedic visit were not considered to have had a CSI. Each participant was followed for 7 days, starting from the date when the orthopaedic consultation was made, and any hospital admissions were recorded. Data were obtained on hospital admissions (dates and discharge diagnoses) from the central CHS database, which includes both hospital diagnoses and diagnoses recorded in the family physician medical record. ACS was considered to have occurred when one of the following diagnoses appeared in the database as a new diagnosis from the admission period: myocardial infarction, ACS, intermediate coronary syndrome, atherosclerosis of coronary artery, coronary artery bypass graft, coronary catheterisation and angioplasty, and unstable angina pectoris.

Statistical analysis

The baseline sociodemographic and clinical characteristics of the study participants were ascertained, using proportions for categorical variables and means and standard deviations for normally distributed continuous variables. Logistic regression was then used to compare the crude and age- and sex-adjusted odds ratio of having an ACS in the week following an orthopaedic visit, between patient visits during which an injection was or was not administered. Because ACS events were rare, the odds ratios approximate risk ratios. Individuals could be included in the analysis more than once, creating correlated observations. Therefore, robust standard errors were used, clustered by patient ID, to calculate appropriate confidence intervals and P-values. Because data sparsity precluded multivariable analysis, potential confounding was addressed through restriction.30 The analysis was repeated while stratifying on cardiovascular risk factors [that is, patients ≥75 years old, smokers, those with pre-existing ischaemic heart disease, hyperlipidaemia, hypertension, obesity, or diabetes, and those with any two or any three of these risk factors]. Finally, several sensitivity analyses were conducted. To explore selection bias, the analysis was repeated including only patients who had...
been admitted to hospital (for any cause) within a week of their orthopaedic visit. The analysis was also repeated using various lengths of hospital stay to define an admission [that is, excluding ‘short’ 1- or 2-day admissions that may have been for elective, pre-planned procedures]. Stata (version 15.1 IC) was used to perform all statistical analyses. All data were anonymised.

RESULTS
Between April 2012 and December 2015, 22,131 patients aged ≥50 years consulted with an orthopaedic specialist (60,856 unique visits). The mean age at the time of the visit was 70.9 years (standard deviation [SD] = 10.8), and 39.1% of the visits were by people aged ≥75 years. Males made 33.6% of visits, and 78.0% had ≥2 cardiovascular risk factors at the time of the visit (that is, obesity, smoking, hyperlipidaemia, hypertension, congestive heart failure, ischaemic heart disease, and diabetes mellitus). CSI was administered in 5.1% of all visits (3075), with 1779 patients having at least one injection over the study period. Patients who had received a CSI were more likely to be older than those who had not [mean age = 74.5 years; SD = 10.3 versus 70.7; 10.8], as well as more likely to have cardiovascular risk factors. Baseline demographic information and cardiovascular risk factors of the cohort participants are presented in Table 1.

All of the orthopaedic visits, 5.4 per 1000 (n = 329) were followed by a hospital admission [all-cause] within 7 days; 7.8/1000 (n = 24) of CSI visits versus 5.3/1000 (n = 305) of non-CSI visits, P = 0.06. Of all visits, 0.4/1000 (n = 25) were followed by an ACS-related hospital admission. CSI visits were more likely to be followed by an acute coronary event, compared with non-CSI visits [2.27/1000 visits versus 0.31/1000, odds ratio [OR] = 7.32; 95% confidence intervals [CI] = 2.81 to 19.11; P<0.0001]. These results remained broadly similar when adjusted for age and sex [OR = 6.62; CI = 2.52 to 17.36; P = 0.0001], as well as when the analysis was restricted to those with cardiovascular risk factors (Table 2).

A series of sensitivity analyses were conducted to assess potential bias. The results remained robust when short hospital admissions (that is, <1 and <2 days long) were excluded, which may have been associated with elective procedures. Finally, the results did not change substantially when the analysis was restricted to orthopaedic visits that were followed by a hospital admission (see Supplementary Table S1 for details).

DISCUSSION
Summary
Receiving a CSI was associated with a seven-fold increase in the risk of a subsequent ACS in an analysis of 60,856 primary care orthopaedic consultations. The results remained robust when cardiovascular risk factors were taken into consideration.

Strengths and limitations
Over 3000 orthopaedic consultations were included in which CSI was administered; to the best of the authors’ knowledge, this is the largest report to date. Routinely collected data from a centralised medical file were utilised, assuring complete electronic capture of events. Finally, some particular features of the Israeli health system (that is, universal healthcare coverage and accessible primary care orthopaedic consultations) increase the validity of the findings; the community- and population-based sample is less prone to the selection bias compared with outpatient-based samples.

This study also has several limitations. Although the procedure of injecting a patient appears clearly in the data records,

### Table 1. Patients’ characteristics at the time of orthopaedic visit by injection administration status

| No CSI, N = 57,781 | CSI, N = 3,075 |
|------------------|--------------|
| Mean age, years (SD) | 70.7 (10.8) | 74.5 (10.3) |
| N, 50–64 (%) | 19,409 (33.6) | 634 (20.6) |
| N, 65–74 (%) | 16,225 (28.1) | 802 (26.1) |
| N, ≥75 (%) | 22,147 (38.3) | 1639 (53.3) |
| N, Male (%) | 19,415 (33.6) | 951 (30.9) |
| N, Obesity (%) | 12,860 (22.3) | 829 (27.0) |
| N, Smoking (%) | 21,559 (37.3) | 1157 (37.4) |
| N, Hyperlipidaemia (%) | 43,989 (76.1) | 2452 (79.7) |
| N, HTN (%) | 27,684 (47.9) | 1760 (57.2) |
| N, CHF (%) | 1541 (2.7) | 81 (2.6) |
| N, IHD (%) | 11,415 (19.8) | 747 (24.3) |
| N, DM (%) | 13,365 (23.1) | 752 (24.5) |
| N, Mean risk factors (%) | 2.7 (1.5) | 3.0 (1.4) |
| N, Mean visits per person (SD) | 3.1 (3.4) | 5.0 (4.1) |
| N, First visit n (%) | 21,443 (37.1) | 504 (16.4) |
| N, Second visit n (%) | 12,360 (21.4) | 509 (16.6) |
| N, Third+ visit (%) | 23,978 (41.5) | 2062 (67.1) |

*Based on inclusion in the CHS chronic disease register (see Supplementary Box S1 for details). *Cardiovascular risk factors: obesity, smoking, hyperlipidaemia, hypertension, congestive heart failure, ischaemic heart disease, and diabetes mellitus. CHF = congestive heart failure. CHS = Clalit Health Services. CSI = corticosteroid injection. DM = diabetes mellitus. HTN = hypertension. IHD = ischaemic heart disease. SD = standard deviation.
Table 2. Acute coronary Syndrome within 7 days of an orthopaedic visit with a corticosteroid injection

| Exposure | N, No ACS | N, ACS | Crude OR (95% CI) | Adjusted OR (95% CI) |
|----------|-----------|--------|-------------------|---------------------|
| All      | No CSI    | 57,763 | 18                | -ref-               | -ref-               |
| All      | CSI       | 30,698 | 7                 | 7.32 (2.81 to 19.11) | 6.62 (2.52 to 17.34) |
| Aged <65 years | No CSI | 19,407 | 2                 | -ref- [P = 0.03]    | -ref- [P = 0.03]    |
| Aged <65 years | CSI    | 633    | 1                 | 15.33 [1.39 to 168.75] | 15.49 [1.40 to 171.65] |
| Aged ≥65 years | No CSI | 38,356 | 16                | -ref-               | -ref-               |
| Aged ≥65 years | CSI    | 2,435  | 6                 | 5.91 [2.07 to 16.83] | 5.95 [2.10 to 16.81] |
| Female   | No CSI    | 38,359 | 7                 | -ref-               | -ref-               |
| Female   | CSI       | 2,121  | 3                 | 7.75 [2.00 to 30.00] | 6.42 [1.72 to 23.89] |
| Male     | No CSI    | 19,404 | 11                | -ref-               | -ref-               |
| Male     | CSI       | 947    | 4                 | 7.45 [1.95 to 28.44] | 6.67 [1.72 to 25.84] |
| No IHD   | No CSI    | 46,563 | 3                 | -ref- [P = 0.10]    | -ref- [P = 0.07]    |
| No IHD   | CSI       | 2,227  | 1                 | 6.64 [0.69 to 63.87] | 6.7 [0.86 to 52.39] |
| IHDa     | NoCSI     | 11,400 | 15                | -ref-               | -ref-               |
| IHDa     | CSI       | 741    | 6                 | 6.15 [2.13 to 17.74] | 6.27 [1.15 to 18.29] |
| No smoking | No CSI  | 36,213 | 9                 | -ref-               | -ref-               |
| No smoking | CSI     | 1,913  | 5                 | 10.52 [3.08 to 35.89] | 8.42 [2.49 to 28.44] |
| Smokingb | No CSI    | 21,550 | 9                 | -ref- [P = 0.07]    | -ref- [P = 0.08]    |
| Smokingb | CSI       | 1,155  | 2                 | 4.15 [0.90 to 19.14] | 4.15 [0.85 to 20.41] |
| No hyperlipidaemia | No CSI | 13,790 | 2                 | -ref- [P = 0.05]    | -ref-               |
| No hyperlipidaemia | CSI | 622    | 1                 | 11.09 [1.01 to 121.85] | 9.03 [0.91 to 90.15] |
| Hyperlipidaemiab | No CSI | 43,973 | 16                | -ref-               | -ref-               |
| Hyperlipidaemiab | CSI    | 2,446  | 6                 | 6.74 [2.37 to 19.21] | 6.22 [1.18 to 17.75] |
| No HTN   | No CSI    | 30,092 | 5                 | n/a                 | n/a                 |
| No HTN   | CSI       | 1,315  | 0                 | n/a                 | n/a                 |
| HTNb     | No CSI    | 27,471 | 13                | -ref-               | -ref-               |
| HTNb     | CSI       | 1,753  | 7                 | 8.5 [3.12 to 23.15] | 8.46 [3.08 to 23.21] |
| No obesity | No CSI  | 44,910 | 11                | -ref-               | -ref-               |
| No obesity | CSI      | 2,261  | 5                 | 9.11 [2.75 to 30.07] | 7.72 [2.36 to 25.24] |
| Obesityc | No CSI    | 12,853 | 7                 | -ref- [P = 0.06]    | -ref- [P = 0.07]    |
| Obesityc | CSI       | 827    | 2                 | 4.44 [0.92 to 21.43] | 4.53 [0.90 to 22.7] |
| No DM    | No CSI    | 44,405 | 11                | -ref- [P = 0.01]    | -ref- [P = 0.02]    |
| No DM    | CSI       | 2,220  | 3                 | 5.22 [1.45 to 18.72] | 4.72 [1.28 to 17.32] |
| DMd      | No CSI    | 13,358 | 7                 | -ref-               | -ref-               |
| DMd      | CSI       | 748    | 4                 | 10.20 [2.48 to 41.94] | 9.55 [2.32 to 39.24] |
| No CHF   | No CSI    | 56,224 | 16                | -ref-               | -ref-               |
| No CHF   | CSI       | 2,987  | 7                 | 8.24 [3.11 to 21.79] | 7.52 [2.84 to 19.90] |
| CHFb     | No CSI    | 1,539  | 1,539             | n/a                 | n/a                 |
| CHFb     | CSI       | 81     | 0                 | n/a                 | n/a                 |
| <2 risk factors | No CSI | 12,912 | 1                 | n/a                 | n/a                 |
| <2 risk factors | CSI   | 455    | 0                 | n/a                 | n/a                 |
| Any two risk factors | No CSI | 44,851 | 17                | -ref-               | -ref-               |
| Any two risk factors | CSI | 2,613  | 7                 | 7.07 [2.69 to 18.57] | 6.92 [2.63 to 18.26] |
| <3 risk factors | No CSI | 25,910 | 1                 | n/a                 | n/a                 |
| <3 risk factors | CSI | 1,083  | 0                 | n/a                 | n/a                 |
| Any three risk factors | No CSI | 31,653 | 17                | -ref-               | -ref-               |
| Any three risk factors | CSI | 1,985  | 7                 | 6.61 [2.51 to 17.37] | 6.76 [2.57 to 17.83] |

*aAll P-values are <0.001 unless specifically stated otherwise. bAnalysis was restricted to patients who were diagnosed with the condition at/before the index orthopaedic visit, as recorded by the Clalit Health Services chronic disease register. cAnalysis was restricted to patients diagnosed with any two or three of the above risk factors. ACS = acute coronary syndrome. CHF = congestive heart failure. CSI = corticosteroid injection. DM = diabetes mellitus. HTN = hypertension. IHD = ischaemic heart disease. OR = odds ratio.
data were not available as to the content, dosage, and medical condition for which the injection was given. The injections have been presumed to be corticosteroids by excluding patients who purchased hyaluronic acid injections prior to their orthopaedic visit; however, it was not possible to differentiate between different corticosteroid products and dosages. It has also been assumed — as the injections were given by orthopaedic specialists — that they were for musculoskeletal conditions affecting soft tissues or joints. It is possible that patients suffering from inflammatory arthropathies, which themselves increase the incidence of ischaemic events, formed part of the patient population. In Israel, however, it is likely that these patients would be treated with CSIs by rheumatologists, rather than by orthopaedic specialists.

Hospital discharge data may have included elective coronary procedures, causing an increase in the number of recorded ischaemic events. However, it was possible to confirm diagnoses by extracting data from two complementary sources using both hospital and primary care records. To assess potential bias introduced by capturing elective cardiac catheterisations as new ischaemic events, the analysis was repeated excluding outcome events associated with 1- and 2-day admissions. The robustness of the association in the sensitivity analysis suggests little bias owing to misclassification of outcome events.

Finally, the relatively small absolute number of outcomes precluded the study from including all potential confounders in a single multivariable analysis. However, it was still possible to consider the possible effect of cardiovascular risk factors through both considering single risk factors and restricting the analysis to higher-risk subgroups: those patients with two and three pre-existing cardiovascular risk factors at the time of their orthopaedic visit. Indeed, physicians may have chosen CSI as a non-operative treatment for those with pre-existing cardiovascular disease or risk factors, as Table 1 suggests. The observed seven-fold increase in risk remained robust after accounting for cardiovascular risk factors, suggesting that CSI was an independent risk factor for an ACS.

Comparison with existing literature
To the best of the authors’ knowledge, this is the first report of an association specifically between CSI and an ACS, although two large population-based studies of oral corticosteroids and all exogenous corticosteroids did show small, significant increases in ischaemic heart disease incidence. Previous reports of outcomes of CSI have generally been small and of low quality, and systemic reviews included fewer patients in total than were injected in this research. It is, therefore, possible that the size of this study enabled findings that have not been demonstrated elsewhere.

The pathophysiological mechanisms by which corticosteroids affect the cardiovascular system have been considered in existing literature. Their potential to exacerbate hypertension, hyperlipidaemia, hyperglycaemia, and coagulopathy are known. In addition, the presence of glucocorticoid receptors in cardiovascular tissues raises the possibility of a localised effect on atherosclerosis. Increases in blood glucose and blood pressure occur primarily in the hours and days following injections. A reduction in blood salicylate levels in the hours following CSI has also been reported, which may have been significant for the ACS patients in this study, the majority of whom had pre-existing ischaemic heart disease and are likely to have been taking aspirin. The existence of these physiological changes in the hours and days immediately after CSI led to the choice of 1 week following injection as the time period for this study.

Implications for research and practice
This study suggests an association between receiving an intra-articular or soft-tissue corticosteroid injection and a subsequent acute coronary event. The large number of CSIs reviewed combined with accurate follow-up has detected an association between a common treatment and a rare and life-threatening side effect, not previously reported. Further research is needed to confirm the association between CSI and ACS, and to identify the patients who are at particular risk. In addition, research should investigate whether all sites of injection are equally likely to trigger ischaemia and whether other orthopaedic injectable products pose similar dangers. In the meantime, it is perhaps necessary to reconsider corticosteroids as a ‘safe’ option, particularly for patients at higher-risk.
REFERENCES

1. McLaindon TE, Barnett RR, Sulliven MC, et al. OARSI guidelines for the non-
surgical management of knee osteoarthritis. Osteoarthr Cartilage 2014; 
22(3): 363–388.

2. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 
2012 recommendations for the use of nonpharmacologic and pharmacologic 
thepathies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012; 
64(4): 645–744.

3. Foster JZ, Voss TT, Hatch J, Frimodig A. Corticosteroid injections for common 
musculoskeletal conditions. Am Fam Physician 2015; 92(8): 694–699.

4. Kaeley GS, Thway M, Dodani S. Injectable corticosteroid use in musculoskeletal 
care specialties. [Abstract]. Arthritis Rheumatol 2016; 68(Suppl 10): https:// 
acrabstracts.org/abstract/injective-corticosteroid-use-in-musculoskeletal-
care-specialties/ accessed 14 Dec 2020.

5. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee 
osteoarthritis (review) summary of findings for the main comparison. Cochrane 
Database Syst Rev 2015; (10): https://doi.org/10.1002/14651858.CD005328.pub3.

6. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid 
injections and other injections for management of tendinopathy: a systematic 
review of randomised controlled trials. Lancet 2010; 376(9754): 1751–1767.

7. Brinks A, Koes BW, Volkers ACW, et al. Adverse effects of extra-articular 
corticosteroid injections: a systematic review. BMC Musculoskelet Disord 2010; 
11: 206.

8. Cheng J, Abi S. Complications of joint, tendon, and muscle injections. Tech 
Reg Anesth Pain Manag 2007; 11(3): 141–147.

9. Kumar N, Newman RJ. Complications of intra- and peri-articular steroid 
injections. Br J Gen Pract 1999; 49(443): 465–466.

10. Platz CM, Knoxston AI, Ragan C. The natural history of Cushing’s syndrome. 
Am J Med 1952; 13(6): 597–616.

11. Maxwell SRJ, Moons R, Kendall MJ. Corticosteroids: do they damage the 
surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 
22(3): 740–753.

12. Kallock E, Neher JO, St. Anna L. Do intra-articular steroid injections affect 
and cardiovascular system? Postgrad Med J 1994; 70(880): 863–870.

13. Ng MKC, Celermajer DS. Glucocorticoid treatment and cardiovascular disease. 
Heart 2004; 90(8): 829–830.

14. Sholiter DE, Armstrong PW. Adverse effects of corticosteroids on the 
cardiovascular system. Can J Cardio 2000; 16(4): 505–511.

15. Sovervein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and 
risk of cardiovascular and cerebrovascular disease in a population based case-
control study. Heart 2004; 90(8): 859–865.

16. Weil L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is 
associated with subsequent cardiovascular disease. Heart 2004; 90(8): 859–865.

17. Kallock E, Neher JD, St. Anna L. Do intra-articular steroid injections affect 
glycemic control in patients with diabetes? J Fam Pract 2010; 59(12): 709–710.

18. Habib GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol 
2009; 28(7): 749–756.

19. Cheng OT, Szuzbanitski D, Vrooman B, Cheng J. Evidence-based knee 
injections for the management of arthritis. Pain Med 2012; 13(6): 740–753.

20. National Institute for Health and Care Excellence. Osteoarthritis: care and 
management. CG177. London: NICE, 2014. https://www.nice.org.uk/guidance/ 
cg177 (accessed 14 Dec 2020).

21. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-
sex-specific mortality for 282 causes of death in 195 countries and territories, 
1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. 
Lancet 2018; 391(10159): 1736–1788.

22. Bachar S, Acis 2010 — Acute Coronary Syndrome Israeli Survey. http://www.e-
med.co.il/emd/new/usersite/presentations/acsis2000/acsis1.asp (access 5 Aug 
2020).

23. Israel Central Bureau of Statistics. Health Survey 2009. General findings. 
2013. https://www.cbs.gov.il/en/publications/Pages/2013/Health-Survey-2009-
General-Findings.aspx (accessed 5 Aug 2020).

24. Kalderon R, Manor O, Abu-Ahmed W, et al. National Program for Quality 
Indicators in Community Healthcare in Israel. 2014–2016 report [Hebrew]. 
2017. https://48fc89f4-e14d-46de-bd30-e76de5f7973e.filesusr.com/ 
ugs/7fa237_b55be6d3c44c54dbf07f1ed27f1567c5.pdf (accessed 21 Dec 2020).

25. Krivy A, Stubbs B, Balicer RD, et al. Low adherence to antidepressants 
is associated with increased mortality following stroke: a large nationally 
representative cohort study. Eur Neuropsychopharmacol 2017; 27(10): 970– 
976.

26. Shmueli L, Shmueli E, Pliskin JS, et al. Second medical opinion: utilization 
rates and characteristics of seekers in a general population. Med Care 2016; 
54(10): 921–928.

27. Eder L, Cohen A, Feldhamer I, et al. The epidemiology of psoriatic arthritis in 
Israel — a population-based study. Arthritis Res Ther 2018; 20(1): 3.

28. Schonmann Y, Ashcroft DM, Iskandar IYK, et al. Incidence and prevalence of 
psoriasis in Israel between 2011 and 2017. J Eur Acad Dermatol Venereol 2019; 
33(11): 2075–2081.

29. Rennert G, Peterburg Y. Prevalence of selected chronic diseases in Israel. Isr 
Med Assoc J. 2001; 3(6): 404–408.

30. Schatz M, Branson RD, Buchman TG, et al. Control of confounding and 
reporting of results in causal inference studies. Guidance for authors from 
editors of respiratory, sleep, and critical care journals. Ann Am Thorac Soc 
2013; 16(1): 22–28.

31. Axial-Zubita JA, Abrahamowicz M, De Vera MA, et al. Immediate and past 
cumulative effects of oral glucocorticoids on the risk of acute myocardial 
infarction in rheumatoid arthritis: a population-based study. Rheumatology 
(Oxford) 2013; 52(11): 68–75.

32. Coelho MCA, Santos CV, Neto LV, Gadelha MR. Adverse effects of 
glucocorticoids: coagulopathy. Eur J Endocrinol 2015; 173(4): M11–M21.

33. Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol 2007; 
157(5): 545–559.

34. Edelman J, Potter J, Hackett L. The effect of intra-articular steroids on plasma 
salicylate concentrations. Br J Clin Pharmacol 1986; 21(3): 301–307.