

Reference	Study Type	Study Dates	Location	Subgroup	Summary	Smoking record	Definition of union	Definition of non-union	Blinding to smoking status	Sex	Age non-smoker mean (range)	Age smoker (range)	mean	Length of FU mean (range)	Censoring	Total lost to follow-up (FU)	Non-smokers lost to FU	Smokers lost to FU	Newcastle Ottawa Score
Adams 2001	Retrospective cohort	1983 - 1995	UK	Fracture TTU	Open tibia fractures with documented smoking history. All Gustilo fracture classifications included. Range of surgery used. Exclusion criteria detailed.	not defined	Weight-bear without pain and radiographic bridging of 3 of 4 cortices on X-rays.	Non-union were fractures that required revision surgery.	-	212 M, 61 F	39.2 (13-90)	38.7 (13-90)	-	-	No	-	-	-	5
Ahmad 2012	Retrospective cohort	2003-2005	UK	Fracture	Treatment of distal tibia fractures with percutaneous locking plates. Metaphyseal fracture with/without intra-articular involvement. Inclusion and exclusion criteria detailed.	not defined	Clinical - fully weight bearing without pain Radiological - visible callus was bridging one cortex on both radiographs.	Non-union >9 months.	-	15 M 3 F	47.9 (16 - 75)	38.1 (20 - 55)	>12 months	-	No	0	0	1	5
Alemdaroglu 2009	Retrospective cohort	2002 - 2007	Turkey	Fractures TTU	Tibial shaft fractures treated with circular external fixator. Fractures resulted from at least one of the following; high-energy injury and/or open fracture and/or comminuted fracture and/or distal extraarticular diaphyseal fracture with obliquity or a butterfly fragment that did not warrant a stable intramedullary fixation. Inclusion and exclusion criteria not detailed.	not defined	Consolidation defined as bridging callus between the main fragments on at least three cortices on AP and lateral x-rays, which was denser than intramedullary canal of the intact bone.	Delayed union >26 weeks. Non-union 52 weeks.	-	-	-	-	>6 months	Yes 2 patients at 52 weeks	2	-	-	5	
Andersen 2001	Retrospective cohort	1993 - 1997	Denmark	Spinal Fusion	Lumbar spinal fusion due to isthmic spondylolisthesis or a degenerative disorder, undergoing a range of treatment options (instrumented and non-instrumented). Exclusion criterion.	self reported	Radiographs Anterior - Posterior and Lateral. A continuous bony bridge on at least one side at the level being fused.	Non-union >2 years.	-	159 M, 237 F	-	-	2 years	-	30 patient excluded due to not responding to smoking questionnaire	0	0	0	5
Assiotis 2012	Prospective cohort	not defined	Greece	Non-union treatment	Tibial delayed and non-union. Several different types of fractures resulted in non-union; simple closed, comminuted closed, range of open fractures.	not defined	Radiographic evidence of bridging callus formation was seen in at least three cortices.	Non-union- absence of either adequate fracture callus >9 month or progression towards healing for 3 consecutive months.	-	27 M, 17 F	-	-	until union or 9 months until non-union defined	-	8 excluded, 5 for loss to FU, 2 non-attendance at outpatients, 1 severe vascular dementia.	-	-	5	
Bednarz 1997	Retrospective cohort	1992-1996	USA	Arthrodesis	Subtalar distraction bone block fusion for the treatment of post-traumatic arthrosis secondary to calcaneal fractures, or subtalar dislocations, or talus fracture, or idiopathic osteoarthritis. Consecutive selection.	not defined	Radiographic analysis	not defined	-	18 M, 14 F	-	-	33 (11-54) months	-	0	0	0	4	
Castillo 2005	Prospective cohort	1994 - 1997	USA	Fracture	Unilateral open tibia fracture. Gustilo IIIA, IIIB and IIIC. Detailed inclusion and exclusion criteria.	consultation	Bridging of the fracture site on the radiograph and the ability for pain free weight bearing.	Non-union >24 months.	-	196 M, 72 F (including 82 previous smokers)	-	-	24 months	-	32	7 (never smoked)	25	5	
Chahal 2006	Retrospective cohort	1995-2002	Canada	Arthrodesis	Subtalar arthrodesis due to 1) hind foot pain was attributable to the subtalar joint. 2) Preoperative diagnosis was either primary or secondary OA. Patients excluded if they had RA or had been treated with a triple fusion. Treatment quite heterogeneous. e.g. iliac crest bone graft used at the surgeon's discretion.	self reported - hospital records	Complete bridging callus or trabeculation across the subtalar joint with no pain when stress was applied to the joint during examination.	Lack of complete bridging callus or trabeculation across the subtalar joint and continued clinical symptoms on joint examination.	blinded	54 M, 34F	-	-	35.5 (10 - 83) months	-	0	0	0	7	
Chang 2006	retrospective cohort	1994 - 2003	USA	Non-union treatment	1,2-intercompartmental supraretricular artery pedicle vascularised bone grafting for scaphoid non-union. Optional scaphoid screws, K wires or both.	self reported	Bridging trabeculae crossing the fracture site on plain radiographs and on CT or trispiral tomograms.	not defined	-	38 M, 9 F	-	-	7.8 (2-49) months	-	2	-	-	5	
Chen 2001	Retrospective cohort	1991-1996	USA	Osteotomy	Ulnar shortening operation for ulnar impaction syndrome. Each side was considered as a separate case. Arthroscopically generally showed tears of triangular fibrocartilage complex and corresponding chondromalacia of the ulnar carpal bones. Osteotomy stabilised with a 5 or 6 holed plate and lag screw.	self reported	Trabeculation across osteotomy site and of confluent bony bridging across both cortices.	Delayed union = incomplete healing at 7 months. Non union lack of progressive healing by 12 months.	-	-	-	-	13.7 months range 4-31 months.	-	14 patients were not considered, 13 as no smoking history in notes and one developed complications that affected union.	-	-	6	
Collman 2006	Retrospective cohort	1994 - 2003	USA	Arthrodesis	Arthroscopic ankle arthrodesis following 6 or more months of conservative treatment. Contraindications were significant ankle joint malalignment, extensive bone loss or poor bone quality, presence of neuropathic joint process or infection. Similar treatment. Consecutive.	self reported - hospital records	Clinical - Fusion site pain, warmth and focal oedema. Radiographs - presence of unequivocal trabeculation across the tibiotalar joint space.	In a few instances, fluoroscopic examination was used to confirm the presence of a non-union.	-	14 M, 25 F	-	-	Clinical FU if union 12 months, non-union average 610 days	-	0	0	0	5	
Dinah 2007	Retrospective cohort	1992 - 2003	UK	Non-union treatment	Treatment of established scaphoid non-union. Patients with incomplete case notes or radiographs were excluded.	consultation	not defined	Non-union - radiographic evidence of a visible fracture line or non-incorporation of the bone graft.	-	32 M, 2 F	27.1 (13.4 - 53.9)	26.4 (17.0 - 37.9)	-	-	0	0	0	5	

Ding 2014	Retrospective cohort	2005 - 2011	China	Fracture	Humeral diaphyseal fracture without sepsis or tumour treated operatively. Gustilo I, II and III. Inclusion and exclusion criteria detailed.	self reported - hospital records	Clinical and radiographic evaluation.	Non-union >9 months.	-	431 M, 228 F	-	-	14.8 (9-24) months	-	0	0	0	4
Dujardin 2007	Retrospective cohort	2001 - 2004	Belgium	Non-union treatment TTU	Delayed and non-union of the tibial shaft from high and low energy injuries, both open and closed tibial proximal, mid and distal tibial fractures; all with concomitant fibular fracture. All treated with a combined partial fibulectomy and an Ilizarov frame without bone graft.	not defined	Complete healing visible on four radiological views.	No non-unions all utilised for time to union.	-	21 M, 7 F	-	-	until union	No	0	0	0	4
Easley 2000	Retrospective cohort	1988 - 1995	USA	Arthrodesis	Isolated subtalar arthrodesis due to post-traumatic arthrodesis following calcaneus fracture, a fracture of the talus, or a subtalar dislocation, primary subtalar arthritis and residual talocalcaneal coalition. Bone graft use optional. Consecutive.	self reported	No pain on stress of subtalar joint. bridging callus or trabeculation on lateral or Broden radiographs.	Continued clinical symptoms with stress applied to the former subtalar joint or lack of bridging callus or trabeculation at the arthrodesis site seen on radiographs.	-	115 M, 59 F	-	-	51 (24-130) months	-	31(32 feet) lost to follow up. 3 died. 4(4 feet) declined to participate. 24 (24 feet) had moved or could not be located. All assessed for radiographic union.	20	11	5
Enninghorst 2011	Prospective cohort	2007 - 2009	Australia	Fracture	Consecutive blunt trauma open tibia fractures and debridement time. High and low energy fractures. All Gustilo-Anderson grades. Wound contamination noted. Range of treatment strategies. Consecutive, inclusion and exclusion criteria detailed.	not defined	Clinical - tender and painful and radiographs bridging of four cortices.	Non-union at 12 months.	-	64 M, 22 F	-	-	12 months	-	-	-	-	4
Fragomen 2012	Retrospective cohort	1999 - 2008	USA	Arthrodesis	Ilizarov ankle arthrodesis using Ilizarov method when cases too complex to be treated by arthrodesis using standard internal fixation techniques. Inclusion and exclusion criteria detailed. Inadequate follow-up were exclude	not defined	Radiographic cortical bridging and loss of lucency	On Ilizarov removal at 6 months Non-union - Clinically: motion at the fusion site on examination. Radiographically: large lucency at the tibiotalar interface.	-	50 M, 41 F	-	-	70 (27-134) months	-	110 originally but only data on 91	-	-	4
Glassman 2000	Retrospective cohort	1992 - 1996	USA	Spinal Fusion	Posterior instrumented fusion at L4-5 or L4-S1. Range of indications. All fusions performed using similar pedicle screw and rod constructs and autologous iliac crest graft.	consultation	Patients without obvious non-union.	Defined based on surgical exploration, hardware failure, 3D CT reconstruction or tomograms.	-	214 M, 155 F	47.1 +/- 13.8	41.2 +/- 9.6	non-smoker 49.4 months smokers 48.7 months	-	34	-	-	6
Hak 2000	Retrospective cohort	1989 - 1997	USA	Non-union treatment	Exchange reamed femoral nailing for femoral diaphyseal non-unions or delayed union after prior intramedullary nailing. Exclusions included patients who developed a non-union after rotational osteotomy, closed femoral shortening, or leg lengthening procedures.	not defined	Clinical - absence of pain and tenderness and ability to fully weight bear Radiological - presence of solidly bridged callus along 4 cortices of the non-union site.	No evidence of healing by 6 months	-	20 M, 3 F	30.1 (17 - 55)	34.53 (21 - 68)	23 (6-70) months	-	0	0	0	5
Hamilton 2007	Retrospective cohort	2001 - 2006	USA	Arthrodesis	Modified lapidus arthrodesis for symptomatic hallux valgus deformity. Patients with clinical or radiological symptoms of non-union 6 months post-operatively were enrolled. Exclusion criteria not detailed.	not defined	Consolidation of the arthrodesis site with obliteration of the joint space and incorporation of the autogenous bone graft.	Clinical - painful, swollen fusion site at 6 months Radiological evidence of failure of bone healing at fusion site after 6 months, broken hardware or both.	-	3 M, 12 F	57 (44 - 71)	54.3 (44 - 59)	6 months	-	0	0	0	
Harvey 2002	Retrospective cohort	1993 - 1998	Canada	Fracture	Gustilo type II, IIIA or IIIB open tibia fractures treated with intramedullary nail or external fixator <8 hours after presentation. Inclusion and exclusion criteria detailed.	consultation	Clinical examination and radiographs showing fracture had united with bridging callus.	Delayed union 6-9 months.	blinded	81 M, 24 F	37 (17-76)	30 (17-71)	union	-	-	0	0	6
Hilibrand 2001	Retrospective cohort	1973 - 1992	USA	Spinal Fusion	Multi-level anterior cervical decompression and fusion procedures with autogenous bone-grafting. Several treatment options including interbody or strut-grafting. Inclusion criteria detailed.	not defined	Radiographs - <1mm change interspinous distance, between flexion and extension radiographs, continuous trabeculation and no intervertebral lucency.	Non-union at 2 years.	-	-	-	-	68 (24-183) months	-	62	-	-	4
Ishikawa 2002	Retrospective cohort	1986 - 1998	USA	Arthrodesis	Hind foot fusion (subtalar, talonavicular, or calcaneocuboid fusion, or a double or triple arthrodesis). Most common reason for surgery was degenerative arthritis and posterior tibial tendon dysfunction. Consecutive.	not defined	not defined	not defined	-	66 M, 82 F	-	-	not defined	-	17 patients from those initially identified	-	-	3
Kyro 1993	Retrospective cohort	1983 - 1991	Finland	Fracture TTU	Isolated tibial shaft fracture treated conservatively with identified smoking history. Low energy, high energy, closed and open fractures.	self reported - hospital records	Clinical and radiological examination.	Non-union and delayed union combined >140 days.	-	100 M, 35 F	-	-	-	No	-	-	1 female excluded	6

Little 2006	Retrospective cohort	1987 - 2003	UK	Non-union treatment	Non-vascularised bone graft with screw fixation for scaphoid non-union and delayed union who had no previous surgery on the fracture were identified from the records.	consultation	Trabeculae seen to cross both bone-graft interfaces on at least 2 views from a 4 – view radiographic series.	not defined	-	not given	26.2 (SD = 7.1)	25.8 (SD = 7.9)	>20 weeks (median 42) unless union had occurred.	-	22 - excluded if defaulted from follow up or failed to respond to subsequent attempts for X-Ray and examination.	11	11	5
Liu 2015	Retrospective cohort	2008 - 2013	China	Fracture	Nonoperative treatment of midshaft (middle three-fifths) of clavicle fractures. Nonoperative treatment. Inclusion and exclusion criteria detailed.	self reported - hospital records	Clinical - absence of mobility or pain on stressing fracture site radiological - evidence of bridging callus, disappearance of the cortical interruption.	Non-union >24 weeks.	-	391 M, 413 F	-	-	24 weeks	-	63 lost to follow-up were excluded	-	-	7
Luszczuk 2013	Retrospective cohort	not defined	USA	Spinal Fusion	Single-level anterior cervical discectomy and fusion (ACDF) with allograft and plate fixation. Range of locking plates and graft types. Inclusion exclusion criteria not given in detail.	not defined	Evidence of bony trabecular bridging between the graft and vertebral body, and if motion was absent on postoperative dynamic images.	Lucency was visualized between the graft and vertebral endplate or when motion was detected at the operative segment.	-	-	-	-	> 24 months	-	A minimum FU of 24 months required for inclusion.	-	-	4
Martin 1999	Retrospective cohort	1998 - 1993	USA	Spinal Fusion	Anterior cervical discectomy followed by arthrodesis with freeze-dried, allograft fibula at one to three levels due to cervical spondylosis, herniated cervical disc or both. Exclusion criterion.	consultation	No movement of the surgically treated level on dynamic radiographs and complete trabecular bridging across both graft-vertebral body interfaces.	Any lucency at graft-vertebral body interface. If multiple levels a psuedoarthrosis at any level counted as non-union.	-	162 M, 127 F	-	-	33 (24-51) months	-	28 did not have follow up to 2 years	-	-	5
McKee 2003	Retrospective cohort	1994 - 1999	Canada	Fracture	Consecutive patients with fracture treated using Ilizarov fixator. Tibiae, femora, humerus, foot and forearms. Range of surgical techniques. All treated included.	not defined	Examined clinically and radiologically.	not defined	-	30 M, 17 F	37.6	38.1	removal external fixator	-	0	0	0	5
Meidinger 2011	Retrospective cohort	2006 - 2008	Germany	Osteotomy	Medial opening wedge high tibial osteotomy with plate for the treatment of unicompartmental knee osteoarthritis. Inclusion and exclusion not detailed. Consecutive selection.	not defined	Radiographic assessment	Clinical - pain over HTO site after 6 months. Radiological - lack of bony consolidation on conventional radiographs at 6 months.	-	142 M, 40 F	-	-	Until union. At 6 months if union not present designated as a non-union.	-	0	0	0	4
Moghaddam 2011	Prospective cohort	2002 - 2005	Germany	Fracture	TTU Isolated tibial shaft fractures. Gustilo I and II without intra-articular inclusion. Exclusion criteria detailed.	self reported - hospital records	Clinical - full pain free weight bearing Radiological - visible bridging on 3 of 4 cortices on AP and lateral radiographs.	Delayed union 4 months Non-union 6 months.	-	61 M, 13 F	41 (18-84)	46 (22-79)	40 (19-64) months	-	20	4	16	5
Murray 2013	Retrospective cohort	1994 - 1997 and 2001 - 2007	UK	Non-union treatment	Displaced diaphyseal clavicle fractures managed nonoperatively if adequate documentation of demographic details and clinical and radiographic follow-up. Inclusion exclusion criteria detailed. Patients with suspected non-union were offered operative open reduction and plate fixation after twenty-four weeks unless they were unfit for surgery.	not defined	Clinical - no or minimal pain, no mobility at the fracture site examination. Radiographic - evidence of bridging callus on radiographs.	Non-union was judged to be present if two of these three criteria remained unsatisfied beyond twenty-four weeks after injury.	-	678 M, 263 F	-	-	until union or operation for non union	-	252 excluded, 44 were excluded due to loss to FU	-	-	4
Perlman 1999	Retrospective cohort	1992 - 1996	USA	Arthrodesis	Ankle fusions. Low energy, high energy and open fractures. Cancellous screws for internal fixation or external fixation. Consecutive.	not defined	Radiographic absence of radiolucent lines and a visualisation of trabeculae crossing the fusion site.	Non-union -some stage after 4 months. Persistence of a complete radiolucency on plain radiographs (in a few cases confirmed with tomograms).	-	37 M, 24 F	-	-	Not given	-	21 of 88 excluded majority due to inadequate radiographs or chart notes confirm union	-	-	5
Ristiniemi 2007	Retrospective cohort	1998 - 2003	Finland	Fracture	Tibial and malleolar fractures treated two ring hybrid external fixation of distal fractures. Moderate to severe soft tissue injury. Exclusion criteria detailed.	not defined	Radiographs showed bridging on 3 of the 4 cortices or the fracture line had disappeared and there was no pain in the fracture upon weight bearing.	Delayed union when an additional operation was required to promote union.	-	27 M and 20 F	-	-	3.4 (2-6) years	-	3	-	-	2
Ruffolo 2015	Retrospective cohort	2005 - 2011	USA	Fracture	High-energy bicondylar tibial plateau fractures treated with dual plating through two incisions. AO/OTA 41-C3.1, 2 and 3; open and closed fractures. Exclusion criteria detailed.	self reported - hospital records	Not defined	Unexpected return to operating room >6 months from index procedure for repeat ORIF.	-	95 M, 45 F	-	-	64.5 (12 - 303) weeks	-	23 lost to follow up were excluded	-	-	4
Schmitz 1999	Retrospective cohort	1990 - 1993	USA	Fracture	Consecutive closed and Grade 1 open tibial fractures. Cast immobilisation, external fixation or intramedullary rod. Detailed inclusion-exclusion criteria.	consultation	Clinical and radiological union.	Non-union lack of clinical union after 1 year of FU.	blinded	73 M, 30 F	35.8 ± 1.9	35.6 ± 1.6	union or > 1 year	-	44	12	32	5

Tay 2014	Retrospective cohort	2003 - 2004 and 2005 - 2006	Australia	Fracture	Femoral and tibial shaft fractures. Gustilo I, II and III without joint involvement or due to pathology. Range of mechanisms of injury. Exclusion criteria detailed.	self reported - hospital records	Clinical - absence of tenderness, weight bear on limb without pain. Radiological - presence of adequate callus bridging the fracture site and disappearance of the fracture line.	Delayed union >6 weeks Non-union >6 months.	-	309 M, 114 F	-	-	12 months	-	-	-	-	4
van Houten 2014	Retrospective cohort	2007 - 2009	Netherlands	Osteotomy	Medial open wedge high tibial osteotomy with medial plate fixation. Autologous graft or bone graft substitute optional. Inclusion and exclusion criteria not detailed (those with sufficient charts/ record data).	not defined	Radiological - systematic review of visibility of fracture line, callus and bridging callus assessed.	Clinical - load-dependent pain, or pain on examination at the osteotomy site. Radiographic - Delayed union predominantly >6 months. Non-union >1 year after surgery.	-	138 M, 47 F	not defined	not defined	Radiographs at 6, 9 or 12 months	1	-	-	-	5
W-Dahl 2004	Prospective cohort	not defined	Sweden	Osteotomy TTU	Tibial hemicallotasis. 2 pins in metaphysis and 2 in diaphysis. Full weight bearing. Orthofix fixator. Distraction started 7-10 days after surgery. Fixator was dynamised at 8 weeks. Consecutive recruitment.	consultation	Radiographs and ultrasound.	Delayed union >16 weeks to remove ex fix.	-	119 M, 81 F	53 (SD 10)	53 (SD 6)	-	No	0	0	0	6
W-Dahl 2007	Retrospective cohort	2000-2005	Sweden	Osteotomy TTU	Hemicallotasis technique for knee deformities based on an external fixator. Inclusion and exclusion criteria not detailed. Consecutive recruitment.	consultation	Radiographic assessment.	Delayed union >16 weeks of ex fix.	-	154 M	54 (SD = 9)	51 (SD = 7)	-	No	0	0	0	6