The limit of tolerable micromotion for implant osseointegration: a systematic review

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Much research effort is being invested into the development of porous biomaterials that enhance implant osseointegration. Large micromotions at the bone-implant interface impair this osseointegration process, resulting in fibrous capsule formation and implant loosening. This systematic review compiled all the in vivo evidence available to establish if there is a universal limit of tolerable micromotion for implant osseointegration. The protocol was registered with the International Prospective Register for Systematic Reviews (ID: CRD42020196686). Pubmed, Scopus and Web of Knowledge databases were searched for studies containing terms relating to micromotion and osseointegration. The mean value of micromotion for implants that osseointegrated was 32% of the mean value for those that did not (112 ± 176 µm versus 349 ± 231 µm, p < 0.001). However, there was a large overlap in the data ranges with no universal limit apparent. Rather, many factors were found to combine to affect the overall outcome including loading time, the type of implant and the material being used. The tables provided in this review summarise these factors and will aid investigators in identifying the most relevant micromotion values for their biomaterial and implant development research.

Metallic protheses implanted directly into bone have revolutionised the treatment of dental, orthopaedic and spinal disease, pain and trauma, with millions of procedures performed annually worldwide. This has resulted in a continued drive from research centres of excellence and industry to develop new technology that improves outcomes, reduces revision rates, and enables treatment for more patients’ groups, such as those that are younger and more active.

In silico and in vitro modelling are at the heart of the pre-clinical development process for new implant technologies. In the field of implant fixation, a common parameter investigated is the amount of oscillatory micromotion at the bone-implant interface. Micromotion is the temporary localised relative movement that occurs between an implant surface and adjacent bone when functional loading is applied; with any permanent displacement known as subsidence/migration. These sub-millimetre (hence micro) motions are too small to be seen by the naked eye. Micromotion is the result of primary implant instability and differing bone/implant material moduli, and consequently depends on the implant material, bone density, implant/bone geometry, surgical technique, and the level of interference fit, as well as the magnitude and direction of the applied loading.

Micromotion is investigated as in vivo data suggest that too much of it leads to failed implant osseointegration: a fibrous capsule forms around the implant rather than a direct structural and functional connection between the host bone and implant. Failed osseointegration leads to aseptic implant loosening, implant failure and the need for expensive revision surgery, both financially and in terms of quality of life. Thus, much research time and resource has been invested to ensure new implant designs and surgical techniques result in acceptable/improved micromotion at the bone-implant interface. There even exists an ASTM standard (F2537–06) to ensure micromotion is measured accurately and repeatably.

Micromotion data are often compared to a limit, below which the implant is considered to pass/be suitable for clinical use, and above which it is considered to be at risk of failed osseointegration. Early in vivo research suggested an upper limit of 150 µm of micromotion and over time this value has become an oft-cited gold standard. However, the evidence in the 1990s for the 150 µm limit was inconclusive and much time has subsequently elapsed meaning that there is likely much more data available with which to draw conclusions about the relationship between micromotion and osseointegration.

This systematic review aimed to compile all the quantitative in vivo evidence relating micromotion to osseointegration to answer the following research questions: (1) Is there value of micromotion that can be universally
used as a limit for in vitro or in silico modelling? (2) To what extent is micromotion correlated with bone-implant contact? (3) Which factors influence the relationship between micromotion and osseointegration?

**Results**

**Study selection and characteristics.** 284 unique records were identified from the databases (Fig. 1). After initial screening, 218 articles were excluded leaving 66 studies for full article screening. An additional 6 studies that passed all inclusion criteria were identified from these 66 studies. After full-text screening, 25 studies were found to be eligible for the quantitative analysis (Table 1).

**Micromotion and osseointegration.** One human and twenty-four animal studies were identified (Table 1). For the human post-mortem study, the micromotion for osseointegrated hip stems was less than 40 µm which compared to 150 µm for a stem with failed bone ingrowth. For the animal studies, the mean value of micromotion for implants that osseointegrated was 32% of the mean value for those that did not (112 ± 176 µm osseointegrated versus 349 ± 231 µm non-osseointegrated, Mann Whitney test \( p < 0.001 \), Fig. 2). However, the osseointegration outcome also depended on other experimental/implant conditions with no distinct osseointegration limit detected. Rather, the range for successful/failed osseointegration overlapped: 15 to 750 µm for osseointegrated samples versus 30 to 750 µm for non-osseointegrated samples (Table 1 and Fig. 2).

**The effects of research method: applied vs measured micromotion.** When micromotion was applied, lower micromotion resulted in more consistent osseointegration (Fig. 3A, Mann Whitney \( p \) value = 0.001). Similarly, when micromotion was measured at the end of the study duration, implants that osseointegrated had lower micromotion than implants that did not (Fig. 3B, Mann Whitney \( p \) value = 0.01). Comparing values of micromotion between the methods (measured vs applied), no differences were observed for the osseointegrated group, and similarly there was no difference between the methods for the non-osseointegrated group. (Fig. 3).
Micromotion and bone-implant-contact.

Out of the 24 animal studies, 13 studies examined osseointegration as the percentage of BIC, 2 studies reported on bone ingrowth and 1 study reported on both BIC and bone ingrowth. For implants that were defined as osseointegrated, a positive correlation was observed between micromotion and % BIC (Spearman’s $\rho = 0.41$, $p$ value = 0.02). Micromotion and BIC were not correlated for the non-osseointegrated group ($p$ value = 0.39), nor the full dataset ($p$ value = 0.07).

Observation time and Bone-implant-contact.

There was a positive correlation between observation time and percentage BIC, with longer study duration time resulting in better percentage BIC (Spearman’s $\rho = 0.40$, $p$ value = 0.01).

Discussion

The most important finding of this systematic review was that the available data refutes the idea of a universal limit of tolerable micromotion for implant osseointegration. Whilst on average, the micromotion associated with osseointegration was 32% of the micromotion associated with failed fixation, many exceptions to the rule were identified (Fig. 2). In some studies, micromotion at the bone-implant interface as high as 750 µm osseointegrated, whilst in other micromotion as low as 30 µm did not osseointegrate. Thus, implant and external factors must be considered when estimating the level of micromotion that could lead to successful osseointegration for a new biomaterial/implant. The following implant factors were associated with higher levels of micromotion and successful osseointegration: hydroxyapatite coating, larger threads in lower density bone, and square pore cross-sectional shape. The following environmental factors were associated with higher levels of micromotion and successful osseointegration: infrequent loading, a rest period following initial loading and longer study duration (9 weeks or more) (Table 2).

The gold standard micromotion limit is often considered 150 µm. However, Overgaard et al., and Soballe et al., showed that this level of micromotion can be tolerated if a period of rest is allowed after initial loading and if the implant was coated with hydroxyapatite. The accelerated resorption of HA coating under excessive micromotion could have led to a better bony ingrowth as studies have previously shown that HA coating on

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Table 1. Osseointegrated (OI) and non-osseointegrated (Non-OI) values of micromotion (µm) from the studies selected. For applied values, the value was set as a controlled experimental parameter, for measured values means and standard deviation are reported where possible. *0 represents experiments with immobilized implants after a period of loading. *12 represents experiments that applied an additional implant displacement for 12 weeks.

| Author          | Year | Country | Micromotion OI (µm) | Micromotion Non-OI (µm) | Applied or measured | Animal or Human |
|-----------------|------|---------|---------------------|------------------------|---------------------|-----------------|
| Aspenberg'92    | 1992 | Sweden  | N/A                 | 500                    | Applied             | Animal          |
| Bragdon'94      | 1996 | USA     | 20                  | 40,150                 |                     |                 |
| Duyck'96        | 2006 | Belgium | 60                  | 30,90                  |                     |                 |
| Goodman a'95    | 1995 | USA     | N/A                 | 500,500                |                     |                 |
| Goodman b'93    | 1993 | Sweden  | 750                 | 750                    |                     |                 |
| Goodman c'94    | 1994 | Sweden  | 500*0               | 500                    |                     |                 |
| Goodman d'93    | 1993 | Sweden  | 500                 | 500                    |                     |                 |
| Jakobsen a'15   | 2015 | Denmark | N/A                 | 500                    |                     |                 |
| Jakobsen b'17   | 2017 | Denmark | N/A                 | 500,500                |                     |                 |
| Jasty'99        | 1997 | USA     | 20                  | 40,150                 |                     |                 |
| Kawahara'03     | 2003 | Japan   | 30                  | 580,630                |                     |                 |
| Overgaard'96    | 1996 | Denmark | 150*0               | 150 *12                |                     |                 |
| Soballe a'92    | 1992 | Denmark | N/A                 | 500,500                |                     |                 |
| Soballe b'92    | 1992 | Denmark | 150                 | 150                    |                     |                 |
| Vandamme a'07   | 2007 | Belgium | 30,50               | 30                     |                     |                 |
| Vandamme b'07   | 2007 | Belgium | 30,90               | N/A                    |                     |                 |
| Vandamme c'08   | 2008 | Belgium | 30,30               | N/A                    |                     |                 |
| Vandamme d'07   | 2007 | Belgium | 30,30               | N/A                    |                     |                 |
| Manley'95       | 1995 | USA     | 33 ± 23.7, 17 ± 4.2 | N/A                    |                     |                 |
| Pilliar'86      | 1986 | Canada  | 28                  | 150                    |                     |                 |
| Trisi a'17      | 2017 | Italy   | 77.9 ± 17.29, 75.3 ± 19 | N/A                   |                     |                 |
| Trisi b'15      | 2015 | Italy   | 64 ± 27             | 177 ± 87               |                     |                 |
| Trisi c'16      | 2016 | Italy   | 94.88 ± 10.94, 60.45 ± 5.29 | N/A                   |                     |                 |
| Trisi d'16      | 2016 | Italy   | 161.26 ± 134.39, 619.5 ± 328.26 | N/A                   |                     |                 |
| Engh'92         | 1992 | USA     | < 40                | 150                    | Measured            | Human           |
titanium implants improve BIC through its direct interaction with osteoblast, osteoclasts and pro-inflammatory markers\textsuperscript{52,53}. Further, previous studies have also shown that a period of rest or otherwise referred to as recovery phase may be beneficial for BIC. The recovery phase or time off helps to counteract the waning effects of long-term mechanical loading, and improve the responsiveness of osteoblasts and osteocytes to restart bone formation\textsuperscript{54,55}. Goodman et al. showed that oscillatory motions up to 750 µm once a day would allow successful osseointegration, while the same motions twice a day would not\textsuperscript{31}, emphasizing the effect of loading duration. Similarly, Goodman also demonstrated how implant factors can influence the tolerable micromotion: by changing

Figure 2. (A) Scatterplot of the animal data showing the micromotion value for osseointegrated (green, circle, n = 28) and non-osseointegrated (hollow circles, n = 23) samples. (B) Violin plot of the same data. Whilst micromotion was lower for the osseointegrated samples (Mann Whitney test $p < 0.001$), there was also considerable overlap between the groups.
the pore-cross sectional shape of the outer bone chamber from round to square in the traditional bone chamber designs, bony ingrowth would be facilitated even with micromotions as high as 500 µm.

Whilst the data reviewed revealed that the mean value of micromotion for successful osseointegration was 112 µm, some studies showed that micromotion as low as 30 µm can lead to failed implant fixation30,40. The authors attributed this to the duration of loading, hypothesizing that the process of bone formation had not been reached within 6 weeks. Subsequent experiments measured osseointegration at 9 weeks or more and demonstrated successful osseointegration with the longer study duration30,44. The data from this systematic review further supports this finding, demonstrating a positive correlation between osseointegration (measured by percentage BIC) and study duration (Fig. 4). Biologically, osseointegration starts with woven bone formation, followed a period of remodelling to lamellar bone in response to mechanical loading. This transition from woven bone to lamellar bone formation takes starts around 6–8 weeks and can take a period of months to complete56,57. Therefore, in vivo experimental studies exploring osseointegration of implants should allow a time period of over 6 weeks to see the full healing response. The effects of study duration have also been reflected by recent computational research which highlighted the differing mechanisms between bone healing and remodelling, and hence the importance of the measurement time point2.

Another explanation for the contradictory in vivo data is that micromotion is a simplified, clinically convenient measure, which overlooks the fundamental mechanobiological mechanisms that drive implant osseointegration. In vivo data coupled with finite element analyses suggest that it is the interfacial stress–strain state resulting from implant micromotion that stimulates osseointegration56,59. Different loading conditions (axial, shear, torsional, etc.), combined with different localised implant/bone geometry lead to different stress–strain states, with too much strain leading to fibrous tissue formation58–61. Indeed, by considering the interfacial stress–strain state, it is possible to relate implant bony ingrowth theory2,58,59 to fracture healing theory62–65, which intuitively one would expect given the involvement of the same cell types66. Conversely, when the implant/environmental conditions that affect the interfacial stress–strain state are ignored, counter-intuitive trends can be observed. For example, when neglecting these factors, it was found that increased micromotion was positively correlated with increased percentage BIC (Fig. 5). However, within study data demonstrate that micromotion and percentage BIC are negatively correlated50. This further emphasises the needs to consider implant and environmental factors and their link to the interfacial stress–strain state when interpreting how micromotion affects osseointegration. It should also be noted that there is no standard interpretation of BIC and so caution should also be applied when interpreting BIC between studies. Some studies report BIC as the fraction of mineralized bone in direct contact with the implant surface64, whilst other describe it as the length of the implant surface in contact with (both mineralised and non-mineralised) bone relative to the total implant length34.

Historically, the causal effect of implant micromotion on osseointegration was investigated by applying known displacement and subsequently measuring osseointegration. However, more recently, research method has shifted to applying known loads and quantifying micromotion at the end of the experiment19. Both measurement techniques were able to identify differences in micromotion between implants that osseointegrated and those that did not. Interestingly, when comparing the results between the two different methods, no differences were found. The majority of studies identified applied micromotion as a controlled experimental condition, meaning that mean and standard deviation micromotion data were not available prohibiting application of the established meta-analysis approaches recommended by Borenstein et al57. For the same reason, it was not possible to perform

Figure 3. (A) Applied values of micromotion in osseointegrated (OI, n = 17) and non-osseointegrated (Non-OI, n = 20) groups for the animal studies. Mann Whitney p value = 0.001 **. (B) Measured values of micromotion in OI (n = 11) and non-OI (n = 3) for the animal studies. Mann Whitney p value = 0.003 **.
| Author       | Year | No. of animals or patients | Species     | No. of samples (per group) | Implant material       | No. of study groups | Implant coating or implant type | Bone                | Time (weeks) | Loading conditions | Loading cycles and time | Micromotion (µm) | Bone ingrowth | Bone–implant contact |
|--------------|------|---------------------------|-------------|---------------------------|------------------------|---------------------|-------------------------------|---------------------|--------------|-------------------|-------------------------|-----------------|----------------|-------------------|
| Aspenberg    | 1992 | 6                         | rabbits     | 13                        | titanium               | 2                   | none                          | Tibia               | 5            | 500 µm micromotion | 20 cycles/day         | N/A             | Unloaded       | Not measured  |
| Bragdon      | 1996 | 20                        | Dogs        | 5                         | Titanium               | 4                   | None                          | Femur               | 6            | UNLOADED          |                         | N/A             | Unloaded       | Not measured  |
| Duyck        | 2006 | 10                        | Rabbits     | 10                        | Titanium               | 4                   | None                          | Tibia               | 6            | Unloaded          |                         | Unloaded        | 20–25%         |                   |
| Good-        | 1995 | 9                         | Rabbits     | 9                         | Titanium               | 4                   | Micromotion alone             | Femur               | 3            | 500 µm micromotion | 40 cycles/day          | 500             | 25 ± 6         |                   |
|              |      |                           |             |                           |                        |                     | polyethylene particles only   |                     | 3            | Unloaded          |                         | N/A             | Unloaded       | 23 ± 9          |
|              |      |                           |             |                           |                        |                     | no polyethylene              |                     | 3            | Unloaded          |                         | N/A             | Unloaded       | 33 ± 6          |
|              |      |                           |             |                           |                        |                     | polyethylene+micromotion     |                     | 3            | 500 µm micromotion | 40 cycles/day          | 500             | 23 ± 9         |                   |
| Good-        | 1993 | 7                         | Rabbits     | 7                         | Titanium               | 3                   | None                          | Tibia               | 7            | 750 µm micromotion | 20 cycles/day          | 750             | 46 ± 5%        |                   |
|              |      |                           |             |                           |                        |                     | 750 µm micromotion            |                     | 3            | Unloaded          |                         | N/A             | Unloaded       | 19 ± 7%         |
| Good-        | 1994 | 5                         | Rabbits     | 5                         | Titanium               | 3                   | None                          | Tibia               | 6            | 500 µm micromotion | 40 cycles/day then unloaded (3 weeks) | 900             | 37 ± 7         |                   |
|              |      |                           |             |                           |                        |                     | 500 µm micromotion            |                     | 3            | Unloaded          | Unloaded               | N/A             | Unloaded       | 20 ± 2          |
|              |      |                           |             |                           |                        |                     |                                     |                     | 3            | Unloaded          | Unloaded               | N/A             | Unloaded       | 37 ± 6          |
| Good-        | 1993 | 10                        | Rabbits     | 6                         | Titanium               | 2                   | Square chamber                | Tibia               | 5            | 500 µm micromotion | 20 cycles/day          | 500             | not measured   |                   |
|              |      |                           |             |                           |                        |                     | 500 µm micromotion            |                     | 3            | Unloaded          | Unloaded               | N/A             | Unloaded       | 500              |
| Jakobsen a   | 2015 | 10                        | Sheep       | 10                        | PMMA                  | 2                   | Femur                         | 12                  | 500 µm micromotion | Every gait cycle     | Unloaded        | 500            |                   |
| Jakobsen b   | 2017 | 10                        | Sheep       | 10                        | PMMA                  | 2                   | Control                       | 12                  | 500 µm micromotion | Every gait cycle     | 500            |               |                   |
| Jasty        | 1997 | 20                        | Dogs        | 5                         | Titanium               | 4                   | Femur                         | 6                   | Unloaded          | N/A                      | Unloaded        | 9.9 ± 2.3      |                   |
|              |      |                           |             |                           |                        |                     | 60                            |                     | 6            | 20 µm micromotion  | 8 h/day               | 20              | 9.0 ± 3.1      |                   |
|              |      |                           |             |                           |                        |                     | 40                            |                     | 6            | 40 µm micromotion  | 8 h/day               | 40              | 11.8 ± 3.9     |                   |
|              |      |                           |             |                           |                        |                     | 150 µm micromotion            |                     | 6            | 150 µm micromotion | 8 h/day               | 150             | 10 ± 4.3       |                   |
| Kawahara     | 2003 | 2                         | Beagles     | 6                         | Titanium               | 3                   | Mordel                        | 6                   | 8 N             | 10 s                      | 30              | 380, 630       | not measured     |
| Overgaard    | 1996 | 14                        | Dogs        | 7                         | Titanium               | 2                   | Hydroxyapatite coated         | Femur               | 16           | 150 µm micromotion | (4 weeks), then unloaded (12 weeks) | Everyday        | 28.5 ± 8.8      | 54.6 ± 10.0     |
|              |      |                           |             |                           |                        |                     | 150 µm micromotion            |                     | 16           | 150 µm micromotion | Everyday              | 150             | 24.1 ± 16.1     | 37.7 ± 10.1     |
| Soballe      | 1992 | 14                        | Dogs        | 8                         | Titanium               | 4                   | Hydroxyapatite coated         | Femur               | 4            | 500 µm micromotion | every gait cycle      | 500             | 0–10%          |                   |
|              |      |                           |             |                           |                        |                     | Hydroxyapatite coated         |                     | 4            | Unloaded          | N/A                      | Unloaded        | 45%            |                   |
|              |      |                           |             |                           |                        |                     | Titanium coated               |                     | 4            | 500 µm micromotion | every gait cycle      | 500             | 0–10%          |                   |

Continued
| Author          | Year | No. of animals or patients | Species | No. of samples (per group) | Implant material | Implant coating or implant type | Bone    | Time (weeks) | Loading conditions | Loading cycles and time | Micromotion (µm) | Bone ingrowth | Bone-implant-contact |
|-----------------|------|----------------------------|---------|----------------------------|-----------------|-------------------------------|---------|--------------|---------------------|---------------------|---------------------|----------------|-------------------|
| Soballe 1982    | 14   | Dogs                       | 7       | 4                          | Titanium        | Unloaded                      | Femur   |              | N/A                 | 130 µm micro-motion | 150                 | 7 ± 2          | 0–10%             |
|                 |      |                            |         |                            | Hydroxylapatite coated | Unloaded         | Femur   |              | N/A                 | 100 µm micro-motion | 30                  |               |                   |
| Van-damme a 2007 | 14   | Rabbits                    | 10      | 3                          | Titanium        | Unloaded                      | Tibia   |              | N/A                 | 150                 | 0                  | 0–20%          |                   |
|                 |      |                            |         |                            | Unloaded         | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
|                 |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
| Van-damme b 2007 | 10   | rabbits                    | 10      | 3                          | Titanium        | Unloaded                      | Tibia   |              | N/A                 | 150                 | 0                  | 0–20%          |                   |
|                 |      |                            |         |                            | Unloaded         | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
|                 |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
| Van-damme c 2008 | 20   | Rabbits                    | 10      | 2                          | Titanium        | Unloaded                      | Tibia   |              | N/A                 | 150                 | 0                  | 0–20%          |                   |
|                 |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
|                |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
| Van-damme d 2007 | 10   | Rabbits                    | 10      | 3                          | Titanium        | Unloaded                      | Tibia   |              | N/A                 | 150                 | 0                  | 0–20%          |                   |
|                 |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
|                 |      |                            |         |                            |                    | Unloaded                      | Tibia   |              | 30 µm micro-motion | 400 cycles/day ; twice/week | 10                  |               |                   |
| Manley 1995     | 12   | Dogs                       | 8       | 2                          | Titanium        | Collared                      | Femur   |              | ± 50 N              | 16 s at 0.5 Hz        | 33 ± 23.7          | 52 ± 11.4      |                   |
|                 |      |                            |         |                            |                    | Collarless                    | Femur   |              | ± 50 N              | 16 s at 0.5 Hz        | 17 ± 4.2           | 42 ± 8.5       |                   |
| Pilliar 1986     |      | Dogs                       | 5       | 3                          | Cobalt Chrome    | Femur                         | 32      |              | 16 s at 0.5 Hz    | 40.49 ± 7.30        | 49 ± 8.5           | 150            |                   |
| Trisi a 2017     | 2    | Sheep                      | 10      | 2                          | Titanium        | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
|                 |      |                            |         |                            |                    | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
| Trisi b 2015     | 4    | Sheep                      | 20      | 2                          | Titanium        | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
|                 |      |                            |         |                            |                    | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
| Trisi c 2016     | 2    | Sheep                      | 10      | 2                          | Titanium        | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
|                 |      |                            |         |                            |                    | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
| Trisi d 2016     | 2    | Sheep                      | 24      | 2                          | Titanium        | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
|                 |      |                            |         |                            |                    | End point analysis            | Femur   |              | 16 s at 0.5 Hz    | 25 N/mm             | 150                 | 0–20%          |                   |
| Engh 1992       | 14   | (6 female)                 | Human   | mean age 71                | Cobalt Chrome    | Femur                         | 32–403  |              | 10 N/kg             | 25 mm               | 150                 | 0–20%          |                   |

Table 2. Detailed study characteristics of the selected studies.
a cumulative meta-analysis to quantify the risk of bias between studies. Rather, to provide some quantitative analysis we applied Mann Whitney tests to the data extracted from each study. Further we isolated the effects of studies that applied micromotion, and those that measured it, and found that this did not affect the principal finding our systematic review (Fig. 3).

In conclusion, this systematic review has demonstrated that the idea of a universal limit of tolerable micromotion for implant osseointegration is misleading. Rather, implant and environmental factors, and their link to interfacial stress–strain states, must be considered to identify the most appropriate limit for the biomaterial/patient group under consideration. The tables provided in this systematic review summarise the implant and environmental conditions for all published quantitative in vivo micromotion research and will enable investigators to compare their data to the most appropriate values.

**Materials and methods**

**Protocol and registration.** Prior to the investigation, the protocol was registered with the International prospective register for systematic reviews PROSPERO (ID: CRD42020196686), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.

**Eligibility criteria.** Studies which fulfilled the following criteria were included: (1) in vivo animal research or post-mortem human data where the implant was inserted pre-mortem. (2) testing of osseointegration when micromotion was either applied or measured with micromotion values reported in the form of displacement (3) the study was an original research article; and (4) the studies were published in English.

Articles were excluded if: (1) micromotion was measured indirectly and/or reported as implant stability quotient (ISQ) or resonance frequency analysis (RFA); (2) Study duration less than 3 weeks; (3) Finite element

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**Figure 4.** Scatter plot graph of the correlation between micromotion values and percentage BIC for the animal studies. For the osseointegrated data (green filled circles) a positive correlation was found (Spearman’s $\rho = 0.41$, $p$ value $= 0.02$). No correlation was observed for the non-osseointegrated data (empty circles), nor the full dataset (all circles).

**Figure 5.** Scatter plot demonstrating the correlation between observation time and percentage BIC for the animal studies. Spearman’s $\rho = 0.40$, $p$ value $= 0.01$. 
Information sources and search strategy. An electronic search was performed for articles published up to 16th November 2020, in the following databases: PubMed, Scopus and Web of Science. The search strategy identified papers which included the following terms: (micromotion OR "micro-motion" OR "micro motion") AND ("osseointegration" OR "osteointegration").

Study selection. Two independent reviewers (N.K., J.S.) assessed the titles and abstracts of all the studies and discarded studies that met any of the exclusion criteria. The full text of all remaining studies was then assessed against the inclusion and exclusion criteria. Any disagreement regarding eligibility of articles were resolved by a third reviewer (R.v.A.).

Data collection process and data items. Data relating to osseointegrated and non-osseointegrated values of micromotion were extracted. The country, animal species, number of study groups, duration of the experiment, implant material and loading conditions were recorded. The outcome of osseointegration measured as bony ingrowth or percentage bone-implant-contact (BIC) were also recorded.

The micromotion methodology (applied or measured) was also recorded. In the applied group, known values of micromotion in the form of cyclic loading were directly applied as a controlled experimental condition and then osseointegration was assessed. In measured group, micromotion was not a controlled experimental condition, rather micromotion at the bone-implant interface was measured once the implant had osseointegrated/not.

Statistical analysis. Data were analysed and plotted using Graph Pad Prism 8 software and have been reported as mean ± standard deviation (SD). Four analyses were performed:

(1) All micromotion values were grouped into osseointegrated/not, according to the definition used by the original study authors. Data were first tested for normality, and then non-parametric Mann Whitney tests were used to compare differences between groups.

(2) Micromotion values were further discretised according to the study method (applied vs measured micromotion). Then analysis 1) was repeated for both of these subgroups.

(3) Spearman correlation tests were used to examine correlation between percentage BIC and micromotion values for three groups: all data, osseointegrated, non-osseointegrated.

(4) Spearman correlation tests were used to examine the correlation between percentage BIC and study duration.

The significance level was set to α = 0.05.

Data availability
Data generated and analysed during this study are included in this published article. Data are available from the corresponding author subject to reasonable request.

Received: 7 January 2021; Accepted: 4 May 2021
Published online: 24 May 2021

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Acknowledgements
This work was supported by UKRI (EPSRC) EP/S022546/1 (N.K. and R.v.A.) and the Peter Stormonth Darling Charitable Trust (J.S.).

Author contributions
N.K. and R.v.A. designed the study. N.K. and J.S. collected and analysed the data. R.v.A. acted as a third reviewer to resolve issues regarding selection of articles for data synthesis. N.K. prepared all the figures and tables. N.K. and R.v.A. designed the study. N.K. and J.S. collected and analysed the data. R.v.A. acted as a third reviewer to resolve issues regarding selection of articles for data synthesis. N.K. prepared all the figures and tables. N.K. and R.v.A. wrote the final manuscript. All authors reviewed the manuscript.

Competing interests
The authors declare no competing interests.

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