Table S1: PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	YES
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	YES
Registration	12	Provide the register name and registration number.	YES

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. accessed on 7 June 2023 [22]

For more information, visit: http://www.prisma-statement.org/

TABLE S2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location /page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1,3, 42,45 Title, Abstract, Intro, Methods, Discussion
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3,Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3,Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4,5, Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3, Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3,4,5, Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4,Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4, Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4,5, Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4,5, Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5, Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6, Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6, Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5,6, Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5,6, Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5,6, Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5,6, Methods

	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5,6, Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5, Methods
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5,6, Methods

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location /page where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7, Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7,Appendix
Study characteristics	17	Cite each included study and present its characteristics.	6-28, Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27-32, Results
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6-28,Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	33-42,Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	33-42,Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	33-42,Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	33-42,Results
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	27-32,Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	33-42,Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	42-45, Disc
	23b	Discuss any limitations of the evidence included in the review.	42-45,Disc
	23c	Discuss any limitations of the review processes used.	42-45,Disc
	23d	Discuss implications of the results for practice, policy, and future research.	44,45,Disc
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1, 3 Abstract, Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	1,3, Abstract, Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3, Abstract
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	45,46
Competing interests	26	Declare any competing interests of review authors.	45,46
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	45

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline f or reporting systematic reviews. BMJ 2021;372:n71.doi: 10.1136/bmj.n71 [accessed on 7 June 2023] [22]

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SUPPLEMENTARY Table S3: Full version of search filters as described by Hooijmans et al. (2010) [23]

Hooijmans,C.R.;Tillema,A.;Leenaars,M.;Ritskes
Hoitinga,M.Enhancingsearchefficiencybymeansofasearchfilterforfindingallstudiesonanimalexperimentationin PubMed. *Lab. Anim.* **2010**, *44*,170–175.https://doi.org/10.1258/la.2010.009117

FIRST PART ("animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms:noexp] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms:noexp] OR "gorilla gorilla"[MeSH Terms] OR "pan paniscus"[MeSH Terms] OR "pan troglodytes"[MeSH Terms] OR "pongo pygmaeus"[MeSH Terms])

SECOND PART OR ((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR

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panda[Tiab] OR pandas[Tiab] OR "wild hog"[Tiab] OR "wild boar"[Tiab] OR fitchew[Tiab] OR fitch[Tiab] OR beaver[Tiab] OR
beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) NOT medline[subset])

SUPPLEMENTARY TABLE S4: Comparative analysis of animal and clinical studies for external validity

STUDY CHARACTERISTICS		ANIMAL STUDIES	CLINICAL STUDY	SCOPE OF TRANSLATION INTO CLINICAL PRACTICE
STUDY POPULATION		-In terms of diet, breeding and housing conditions, all studies had a homogenous population. -Metabolic indices and other parameters were checked at the same time of the day for all animals. -Animals in individual studies were operated on by the same investigators following identical methodological protocol.	24 patients of ages b/w 45 and 65 years were enrolled at the beginning of the study with inclusion criteria such as: - body mass index 20-30 kg/m2 -T2D present for more than 5 years. -glycosylated Hemoglobin (HbA1c) of 7%-10% with insulin treatment. -Fasting blood glucose (FBG) was 7.5-12 mmol/liter -Insulin injections given for not less than 1 year and more than twice a day. -daily dose of insulin was >/ 0.4 IU kg/d -Transplantation of SHED from same cell preparation and using identical procedural protocol.	-Animal and clinical study consisted of a relatively uniform population, and used uniform procedural protocol. -Diabetes Mellitus is prevalent in a wide range of patients in terms of genetic and environmental factors such as socioeconomic factors, diet, habits, compliance issues and attitude to treatment. -Scope of therapeutic effects of DSCs, success of therapy and translation potential into clinical practice can be gauged after more clinical studies are performed which include a greater number and range of diabetic patients. Animal studies which reflect the diversity of human diabetic patients should be performed and published.
SPECIES OR PARTICIPANT SELECTION / CO-		6 studies used Sprague Dawley	Study had extensive exclusion criteria such as:	Genetic variations between

MORBIDITIY CONSIDERATIONS		(SD) rats; 2 studies used Goto Kakizaki (GK) rats; 2 studies used Wistar rats; 1 used Fischer 344 rats. 2 studies used BALB mice; 4 studies used C57BL/6 mice.	-gestational DM or lactating females. -acute complications of DM -Recipients of SC treatment. -hypertensive patients. -Patients with other major systemic illnesses. - Concurrent medication such as corticosteroids, and immunosuppresants. - presence or history of tumors.	strains can cause study outcomes to be missed or magnified. Hence selection of an appropriate animal is essential and larger sample power is required. -Rodents are used in animal studies because although their life span is much shorter, the stages of their life follow those of humans closely. - Within the C57BL6 strain, there exists diversity in response to a high fat diet. -Although the human study included exclusion criteria that were consistent with many clinical studies, due to the vast number of co-morbidities that exist with DM, in clinical practice DSCs may have results that vary from those reported in the study. -Safety during concurrent use of medications and pregnancy should also be studied for DSC therapy to be successfully translated to clinical use.

GENDER OF ANIMALS/ PARTICIPANTS		One study included female mice; all other studies used male animals.	Number of males and females enrolled in the study was unclear.	- Due to effects of sex hormones, some diabetic rodent models exhibit gender differences in terms of response to injury and subsequent treatment. -In humans, although T1DM and T2DM are more commonly diagnosed in males, diabetes in general is widely prevalent in males *and* females. -Clinical studies should include males and females to reflect the universality of the disease. Gender variations in terms of complications and response to treatment should be explored.
AVERAGE AGE OF STUDY POPULATION AND TIME OF DISEASE INDUCTION		Age of animals ranged from 5- 16 weeks old at the time of DM induction. Dental stem cell treatment was given at a time that ranged from 0th day to 48 weeks following disease induction.	Patients were 45-65 yrs of age at the start of study. Study included patients having T2DM for greater than 5 years and required more than 2 injections of insulin daily.	While T1DM is typically seen in younger patients, T2DM tends to present later in life. The use of appropriately aged animals and humans would better reflect the disease in humans. Success of therapy is dependent on the

				time of therapeutic intervention. The clinical study appropriately included patients with a more chronic form of DM. Omi et al (2017) illustrated the effects of DPSC therapy 48 weeks after DM was induced. This study may be considered as an aging animal model wherein the therapeutic intervention was carried out at a later stage of life in the animals. .
DURATION OF EXPERIMENT AND TREATMENT IN STUDY		Duration of the experiment i.e from disease induction to animal sacrifice ranged from 4 weeks to 52 weeks. Duration of treatment i.e. from the time of SC transplantation to animal sacrifice ranged from 20 days to 16 weeks.	Study consisted of screening period (1 week), treatment period (6 weeks) and follow up period (12 months after last SHED transplantation) Parameters were assessed during treatment and follow up periods.	-The duration of animal studies should be such that the results can be extrapolated to clinical practice. - Similar to humans, some animals undergo various stages of the disease following disease induction which may affect the end points in the study. Hence, long terms as well as studies of short duration are important to aid in understanding the interplay between disease and its treatment in humans at each

				stage of disease. -One study (Hata 2021) demonstrated the effects of hDPSC on diabetic neuropathy in BALB mice at 16 weeks following hDPSC transplantation, which may be considered as long term effects of hDPSC therapy in a rodent model.
PARAMETERS ASSESSED IN STUDY		Body weight, blood glucose, histopathology and immunochemistry Behavioural tests such as tail flick test, thermal plantar test Tests for diabetic neuropathy such as SNCV,MNCV, SNBF. Renal function tests for nephropathy, urine glucose, creatinine Inflammatory markers such as IL-1alpha, TNF, CRP	continuous glucose monitoring, HbA1c, Fasting blood glucose, daily insulin dose requirements, C-peptide level for insulin release, HOMA-IR, urine and blood panels, with daily insulin dose being the primary parameter of treatment efficacy.	- Unlike in animal experiments, the pancreas and other organs in humans cannot be removed to histologically verify the success of the treatment. Nevertheless, histological studies of pancreatic islets in animal studies are important to determine β-cell mass and insulin content. - Mice tend to have higher blood glucose concentrations than humans. Hence, definitions for DM should be appropriately applied in rodent models. - Parameters should be standardized to monitor efficacy of SC treatment in humans.

				- Similar to human studies and in clinical practice, the most common parameter that is tested in DM animal models is blood glucose. - As therapy can cause toxicity and reduced appetite which in turn can cause a decrease in blood glucose and weight loss, in DM animal models especially in T1DM, body weight is an essential parameter to eliminate the possibility that the reduction in serum glucose is because of drug toxicity rather than successful therapy.
METHOD OF DIABETES INDUCTION		DM was induced either by STZ or with high fat diet or by both.	All patients included had T2DM.	STZ induced DM which is chemically induced DM is the most common method to induce T1DM in animal models. However it can be toxic to other organs in the body and this should be considered while interpreting results. Regeneration of pancreatic cells is sometimes observed following STZ treatment. STZ can also cause changes in T-regulatory cells which may affect the results of the

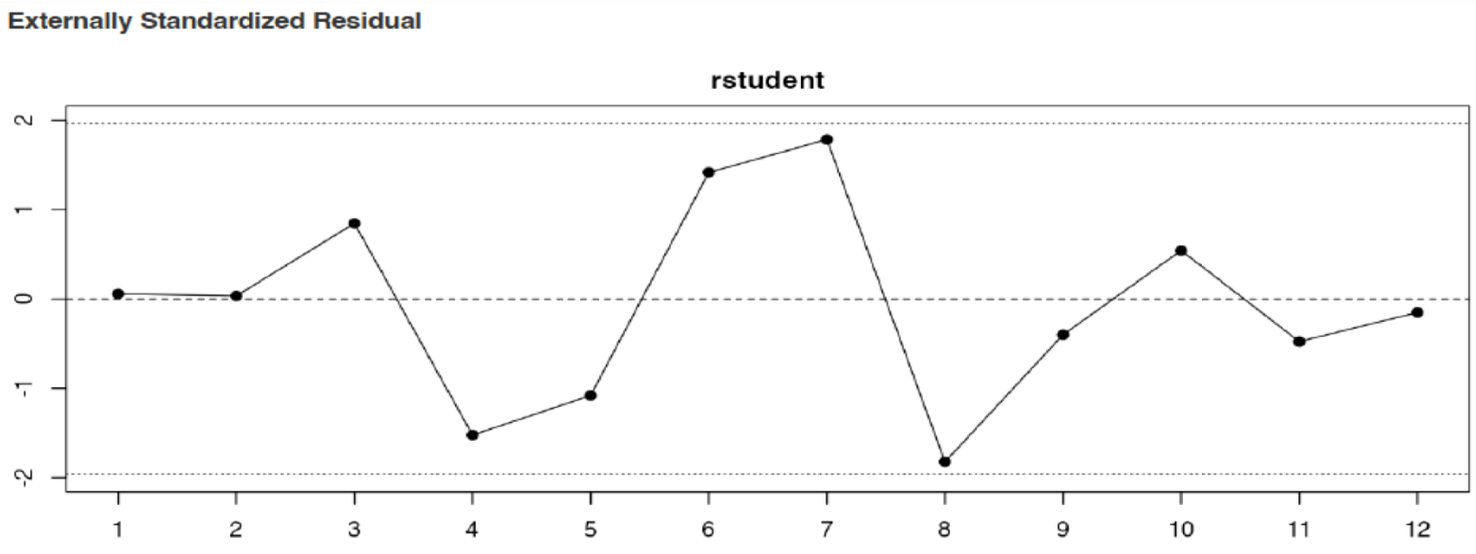
				treatment. -Not all T2DM patients are obese, and hence it is important that DSC treatment efficacy in lean animal models of T2DM is also studied.
SOURCE OF STEM CELLS		4 studies used hDPSCs, 6 used SHED, 1 used hGMSCs, 3 used rat DPSCs, 1 used mice DPSC. One study used hPDLSCs. Autotransplantation was not performed.	SHED from naturally exfoliated teeth from human donors without invasive procedures after passing tumorigenic and bio safety tests.	-If translated into clinical practice, the choice of source of DSCs is essential not only in terms of efficacy, but also for graft rejection. Autotransplantation may be a viable option to avoid these issues. -Age of the tooth selected for stem cells, presence of caries and pulpal involvement and history of invasive procedures done on the tooth may affect stem cell viability. Comprehensive examination and testing should be done to check tooth viability in clinical practice. - Animal studies which used rodent DSCs, used animals from the same species and strain. Whether DSCs from another species can be used to treat DM in humans with minimal complications needs to be

				explored.
MODE OF STEM CELL ADMINISTRATION/CHOICE OF DSC DELIVERY		Routes of DSC administration included IV, IM, SC, intraperitoneal, intrapancreatic, and underneath the kidney capsules. Either single or repeat doses of DSCs were administered. Studies used freshly prepared or cryopreserved stem cells.	Study used IV mode of administration for SHED infusion 3 times over 42 days.	Hata et al (2015) reported that parameters improved in both freshly isolated as well as cryopreserved DSCs. More human studies that ascertain whether viability of DSCs remains for a longer period of time, and determine possible methods of storage of SCs will be useful in clinical practice, especially while considering autotransplantation. Complications following each route of administration in humans should be determined for successful translation. Engrafted DSCs were found in muscles, kidneys and liver. In humans, whether this would be a undesirable effect due to possible tumorigenic effects needs to be further investigated. Due to chronicity of DM, in terms of long term efficacy and potential for translation to clinical practice, more clinical studies should be conducted to

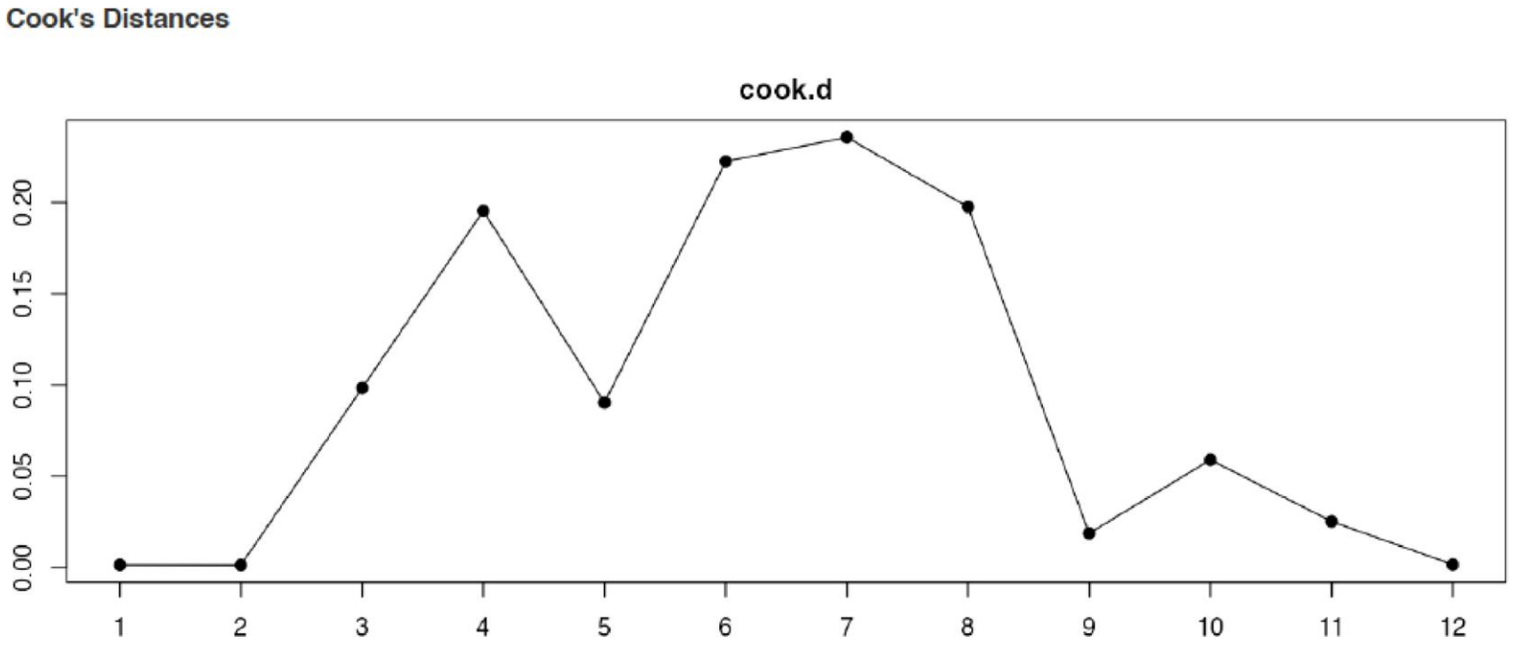
				determine for how long the effect of SCs lasts after administration.
DOSE OF STEM CELLS ADMINISTERED		Dose of DSC administration varied among animal studies.	0.1 U/ Kg body weight. Each unit contained 1 x 10^7 SCs	The dose of DSCs administered in the human study was determined based on previous clinical research of mesenchymal stem cells from sources other than teeth. Since the appropriate dosage and concentration depends on numerous patient and treatment factors, the effective dose for DM in humans requires further research.
RESULTS		All studies reported improvement in parameters with DSC treatment over varying periods of time.	Most parameters improved during and after treatment period over 12 months. Fasting blood glucose reduced during treatment period (42 days) but increased during follow up although changes were not statistically significant. Out of 24 patients enrolled at the start of study, 2 quit during follow up period. 7 patients required less or no daily insulin during and after study.	One animal study (Omi et al 2017) reported that parameters improved in long term DPN (52 weeks from time of disease induction), suggesting that SC treatment may be viable even in DPN which has been diagnosed at a later stage. Another animal study reported that DPN parameters improved 16 weeks after transplantation (Hata et al 2021), suggesting that SC treatment may be effective as a long

				term form of therapy. Patient compliance is an important factor to consider for treatment to be successful and cannot be taken into account for animal studies. Since it has not yet been established whether multiple doses are required to obtain therapeutic efficacy, follow up appointments are imperative for this form of treatment.

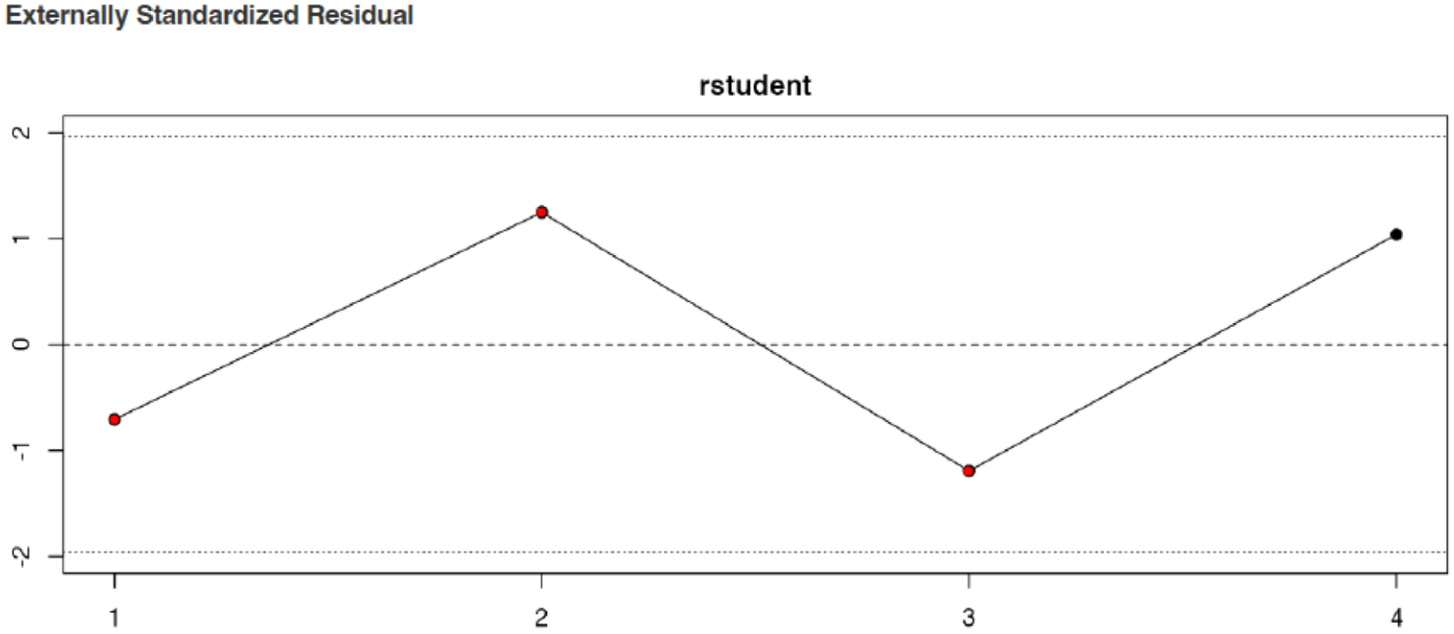
Studentized t residuals: Effect of DSCs on blood glucose



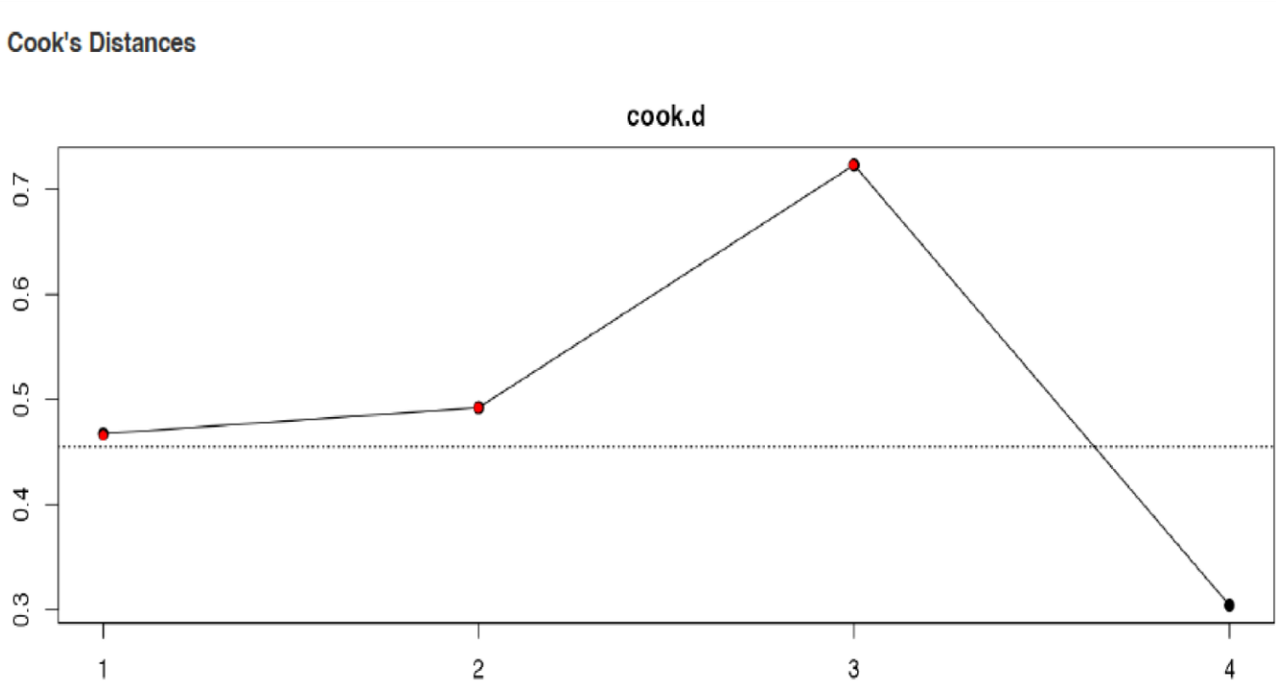
Cook’s distances: Effect of DSCs on blood glucose



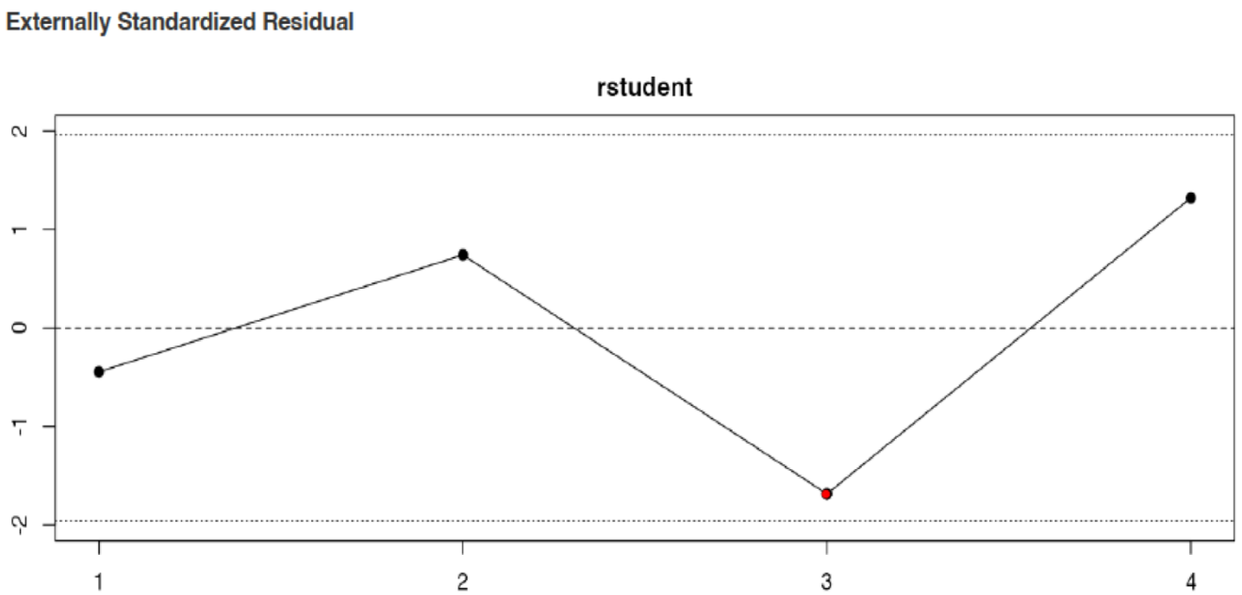
Studentized t residuals: Effect of DSCs on SNCV



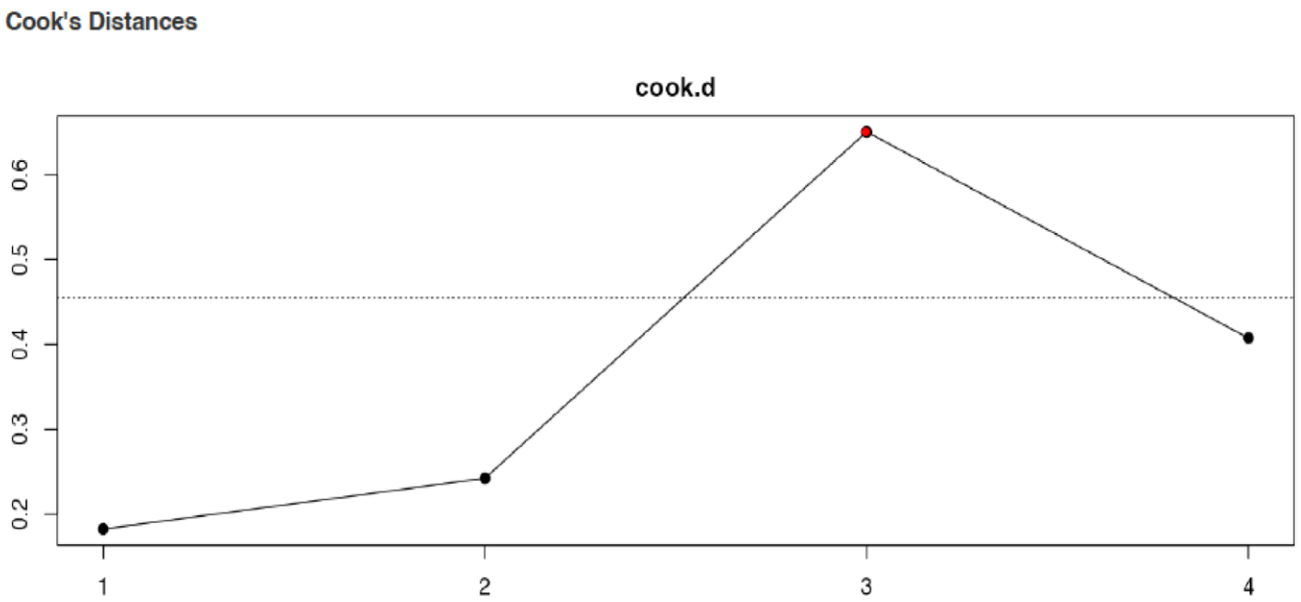
Cook’s distances:Effect of DSCs on SNCV



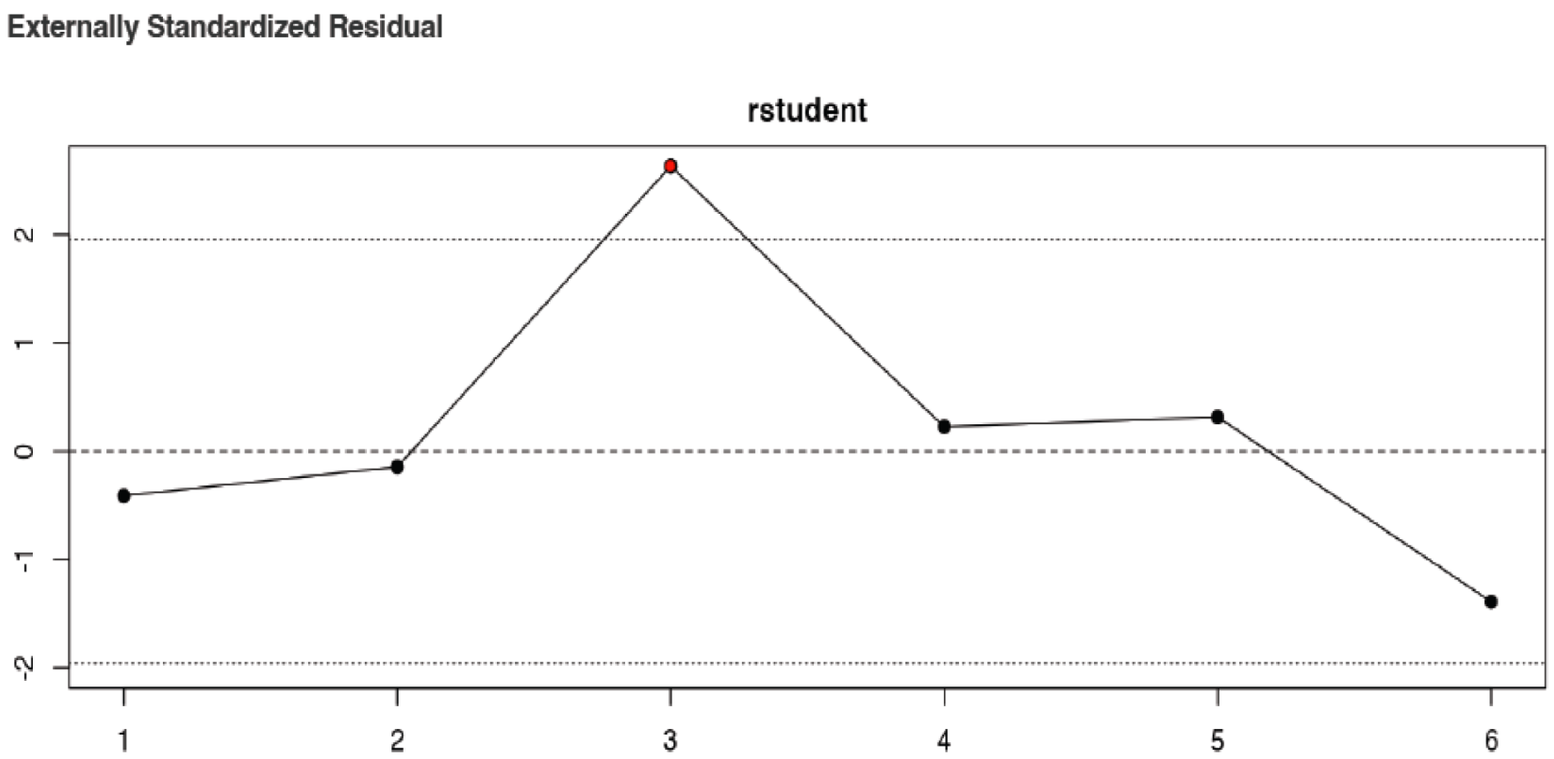
Studentised t residuals: Effect of DSCs on MNCV



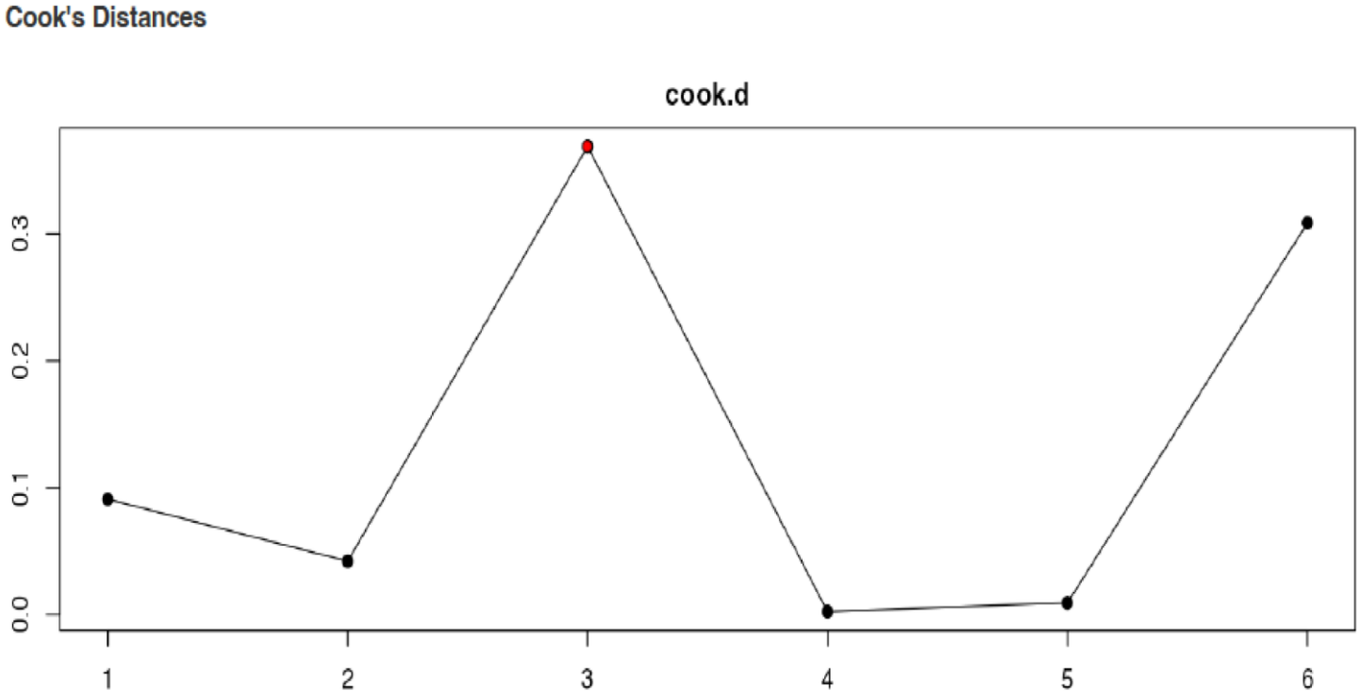
Cook’s distances: Effect of DSCs on MNCV



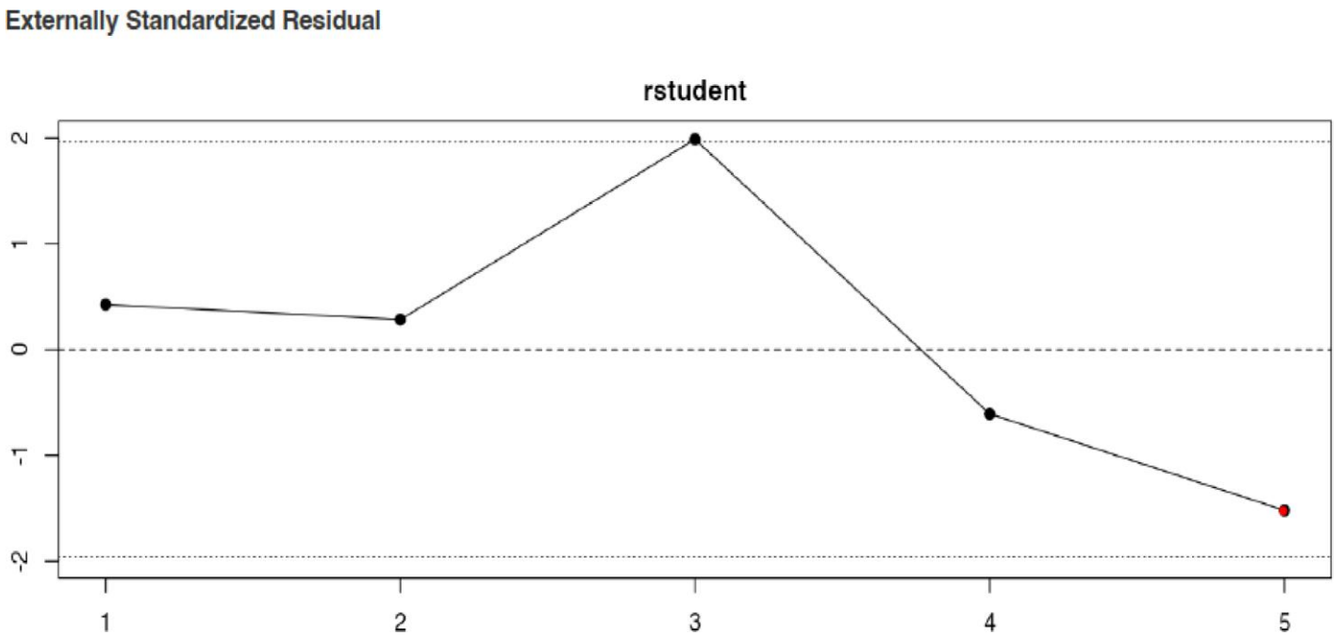
Studentized t residuals: Effect of DSCs on Capillary/Muscle ratio



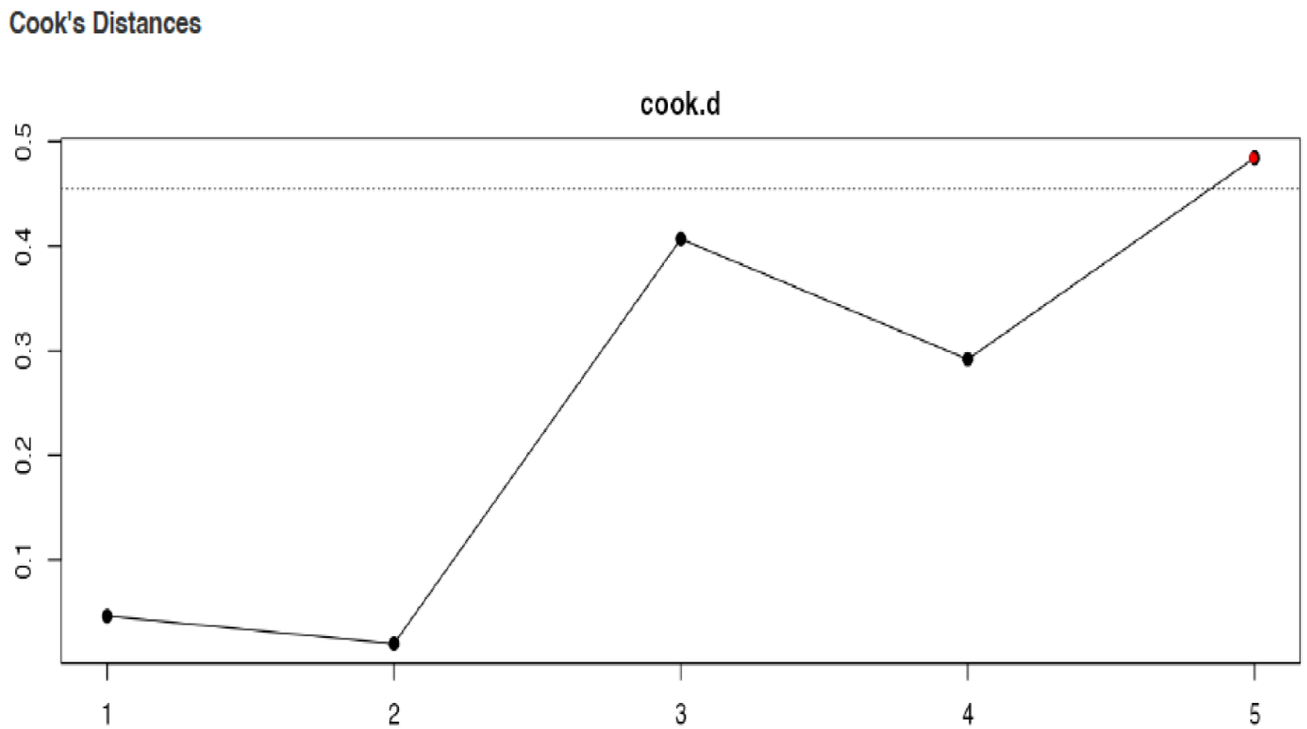
Cook’s distances: Effect of DSCs on Capillary/ Muscle ratio



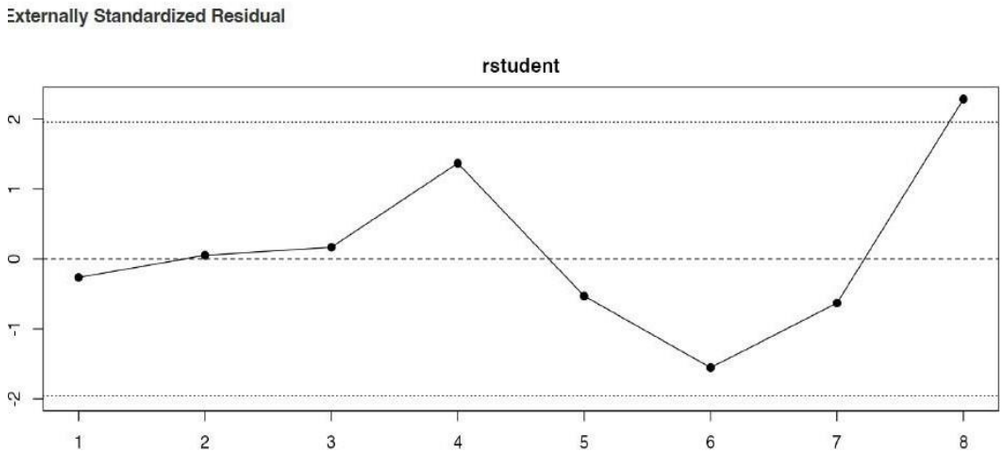
Studentized t residuals: Effect of DSCs on IENFD



Cook’s distances: Effect of DSCs on IENFD



Studentized t residuals: Effect of DSCs on body weight



Cook’s distances: Effect of DSCs on body weight